

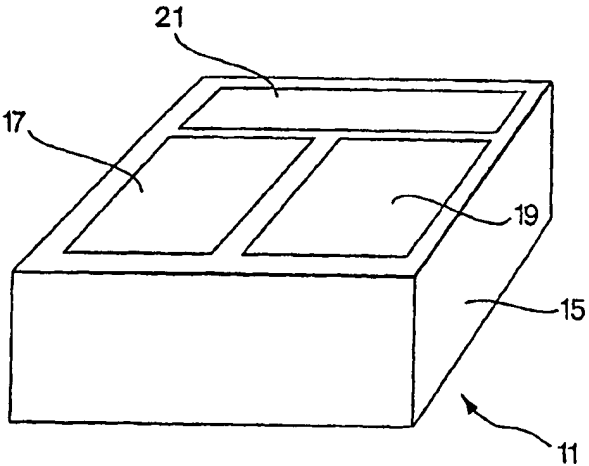
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<p>(54) Title: FATTY ACID-ANTICANCER CONJUGATES AND USES THEREOF</p> <p>(57) Abstract</p> <p>The invention provides conjugates of fatty acids and anticancer agents useful in treating cancer, and compositions and formulations thereof. Methods for using the conjugates are also provided.</p>		
		

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**FATTY ACID-ANTICANCER CONJUGATES AND USES THEREOF****Field of the Invention**

The invention relates to conjugates of fatty acids and anticancer agents useful in treating  
5 cancer, and compositions and formulations thereof. Methods for using the conjugates also are  
provided.

**Background of the Invention**

Improving drug selectivity for target tissue is an established goal in the medical arts. In  
10 general, it is desirable to deliver a drug selectively to its target, so that dosage and, consequently,  
side effects can be reduced. This is particularly the case for toxic agents such as anti-cancer agents  
because achieving therapeutic doses effective for treating the cancer is often limited by the toxic  
side effects of the anti-cancer agent on normal, healthy tissue. The problems relating to lack of  
drug selectivity can be exemplified by Taxol.

15 Taxol® (paclitaxel) was first isolated in 1971 from the bark of Taxus brevifolia and was  
approved in 1992 by the US Food and Drug Administration for treatment of metastatic ovarian  
cancer and later for breast cancer. Its mechanism of action is believed to involve promoting  
formation and hyperstabilization of microtubules, thereby preventing the disassembly of  
microtubules necessary for completion of cell division. It also has been reported that Taxol  
20 induces expression of cytokines, affects the activity of kinases and blocks processes essential for  
metastasis, in as yet uncharacterized mechanisms of action.

Taxol has attracted unusually strong scientific attention, not only because of its unique  
antiproliferative mechanism of action, but also because it is active against nearly all cancers  
against which it has been tested and because it has been discovered to be an analog of numerous  
25 closely related compounds occurring naturally. These compounds, taxanes, are now recognized  
as a new class of anticancer compounds.

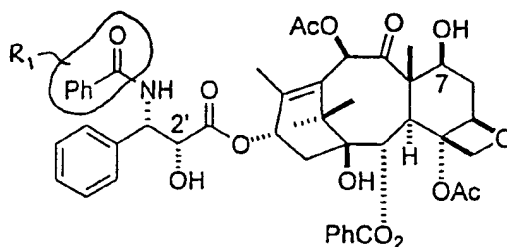
Taxol's strength against cancers of diverse tissue origin also represents a significant  
drawback. An ideal anticancer agent has tissue specificity, thereby reducing side-effects on normal  
(dividing) cells. Taxol analogs with tissue specificity therefore are desired. Another drawback  
30 of Taxol is its extreme insolubility. Taxol can be administered effectively in a solvent including  
Cremophor® EL (polyoxyethylated castor oil), which combination can provoke severe  
hypersensitive immune responses. As a result of these drawbacks, and also as a result of the

-2-

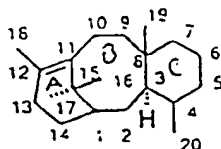
potential for modifying Taxol at numerous sites as demonstrated by other naturally-occurring taxanes with anticancer activity, a search for more selective taxanes was launched.

To date, more than 200 taxanes have been synthesized (or isolated) and tested *in vitro* or *in vivo* for anticancer activity. The results, however, have been so disappointing that the National Cancer Institute (NCI) generally no longer is interested in testing Taxol analogs. In general with Taxol analogs, the solubility problems remain, and/or potency is sharply reduced, and/or selectivity is not improved, and/or the ratio of the median toxic dose to the median effective dose ("therapeutic index") is unacceptably reduced.

Taxol has the following formula:



Taxanes have the basic three ring structure (A, B and C), substituted or unsubstituted. Taxol's carbons are numbered conventionally as follows:



Based upon the taxanes tested to date, as many questions have been raised as have been answered, and general rules have not been fashioned easily in predicting selectivity, activity and solubility. Firstly, no rules have emerged regarding selectivity. Those taxanes that are strongly active appear to have activity as broad as Taxol's activity, and no headway appears to have been made in terms of developing a more selective Taxol analog.

Some information about activity has emerged. Numerous substitutions have been made at C7, C9, C10, C19, R<sub>1</sub> and combinations thereof while retaining significant, but usually reduced, activity. Substitutions at C2, C4 and 2'OH, however, are generally not tolerated. These conclusions are only generalities, for example, because some substitutions at C9-C10 (cyclic derivatives) are not tolerated and some substitutions at C2 (meta substitutions on the phenyl) are tolerated. Likewise, the C13 side chain and, in particular, the 2'OH are required, although the

minimum structural requirements of the side chain have not been determined for therapeutic efficacy.

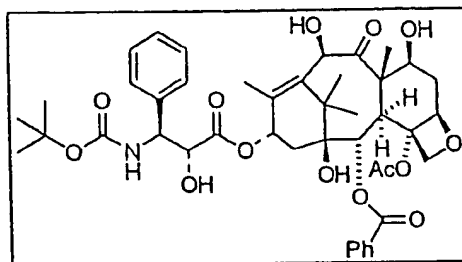
Attempts to improve Taxol's solubility have not resulted in successful clinical products. One approach has been to manufacture prodrugs of Taxol, which prodrugs undergo *in vivo* transformation into Taxol and some other product. Attempts were made to esterify the C7 hydroxy and 2' hydroxy groups, with the hope that the bond would be stable in solution (to permit preferred administration modes - i.v. over at least 24 hours) but would cleave readily *in vivo*. The groups tested were all hydrophilic and included amines, short carboxylic acids (using e.g. succinic anhydride and glutaric anhydride), sulfonic acids, amino acids and phosphates. Generally, activity was reduced although some success was obtained with certain derivatives. Again, no particular pattern emerged permitting one to predict reliably which groups could be substituted on Taxol to yield a therapeutically useful product, although it was suggested that the 2' OH derivatives may cleave more easily than the C7 OH derivatives.

Several other factors add to the problem of predicting which Taxol analogs will be effective. Multiple mechanisms of action have been proposed in the literature, and a change in one position may have no effect on activity on one such mechanism but may eliminate activity on another mechanism. In addition, changes that favorably influence activity may unfavorably influence bioavailability. For example, Taxol affects microtubule formation inside a cell, but a change in structure that increases intracellular activity may adversely affect the ability of Taxol to gain entry into a cell. Taxol also is known to bind to proteins, and the effect on activity that results from a change in Taxol's binding to protein (in terms of conformation, cellular absorption and solubility) is unknown.

It has been reported that Taxol does not get into the brain, apparently excluded by the blood brain barrier. It is not known why this is so, as Taxol is lipophilic, gets into cells and might be expected to cross the blood brain barrier.

Among the most promising of the two hundred analogs tested is Taxotere® (docetaxel), because of its slightly increased activity and solubility. Oddly, however, Taxotere differs from Taxol at sites which typically do not have a strong influence on activity, and one would not predict the improvements in Taxotere from these differences, even in hindsight.

Taxotere has the following formula:



Fatty acids previously have been conjugated with drugs to help the drugs as conjugates cross the blood brain barrier. DHA (docosahexaenoic acid) is a 22 carbon naturally-occurring, unbranched fatty acid that previously has been shown to be unusually effective, when conjugated to a drug, in crossing the blood brain barrier. DHA is attached via the acid group to hydrophilic drugs and renders these drugs more hydrophobic (lipophilic). DHA is an important constituent of the brain and recently has been approved as an additive to infant formula. It is present in the milk of lactating women. The mechanism of action by which DHA helps drugs conjugated to it cross the blood brain barrier is unknown.

Another example of the conjugation of fatty acids to a drug is the attachment of pipotiazine to stearic acid, palmitic acid, enanthic acid, undecylenic acid or 2,2-dimethyl-palmitic acid. Pipotiazine is a drug that acts within the central nervous system. The purpose of conjugating pipotiazine to the fatty acids was to create an oily solution of the drug as a liquid implant for slow release of the drug when injected intramuscularly. The release of the drug appeared to depend on the particular fatty acid selected, and the drug was tested for its activity in the central nervous system.

Lipidic molecules, including the fatty acids, also have been conjugated with drugs to  
25 render the conjugates more lipophilic than the drug. In general, increased lipophilicity has been  
suggested as a mechanism for enhancing intestinal uptake of drugs into the lymphatic system,  
thereby enhancing the entry of the conjugate into the brain and also thereby avoiding first-pass  
metabolism of the conjugate in the liver. The type of lipidic molecules employed have included  
phospholipids, non-naturally occurring branched and unbranched fatty acids, and naturally  
30 occurring branched and unbranched fatty acids ranging from as few as 4 carbon atoms to more  
than 30 carbon atoms. In one instance, enhanced receptor binding activity was observed (for an  
adenosine receptor *agonist*), and it was postulated that the pendant lipid molecule interacted with

molecule interacted with the phospholipid membrane to act as a distal anchor for the receptor ligand in the membrane micro environment of the receptor. This increase in potency, however, was not observed when the same lipid derivatives of adenosine receptor *antagonists* were used, and generalizations thus were not made possible by those studies.

5

### Summary of the Invention

We have discovered that conjugation of fatty acids to anticancer compounds to form a fatty acid-anticancer compound conjugate reduces toxicity of the anticancer compounds, and increases anticancer compound effectiveness in inhibiting cancer proliferation as compared to the unconjugated anticancer compounds.

We have discovered that a fatty acid-anticancer compound conjugate appears to be confined, unexpectedly, to the plasma space of a subject receiving such treatment, and that the conjugate has, suprisingly, (i) a smaller volume of distribution as compared to the unconjugated anticancer compound alone (in many instances ~100 fold less), and (ii) a smaller clearance as compared to the unconjugated anticancer compound alone (in many instances ~100 fold less). Moreover, also unexpected was the discovery that the fatty acid-anticancer compound conjugate was present at a higher concentration in tumor cells as compared to the unconjugated anticancer compound.

According to one aspect of the invention, a fatty acid-anticancer compound conjugate composition for administration to a subject is provided. The composition includes at least one fatty acid-anticancer compound conjugate in a container for administration to a subject. The amount of the fatty acid-anticancer compound in the container is at least about 10% greater than the maximum tolerated dose (MTD) for the unconjugated at least one anti-cancer compound (based on the weight of the anticancer compound in the conjugate versus the weight of the anti-cancer compound itself, or calculated on a molar basis of the conjugate versus the unconjugated anti-cancer compound). Preferably the amount of the fatty acid-anticancer compound in the container is at least about 20% greater than the MTD, 30% greater than the MTD, 40% greater than the MTD, 50% greater than the MTD, 75% greater than the MTD, 100% greater than the MTD, 200% greater than the MTD, 300% greater than the MTD, or 400% greater than the MTD for the unconjugated at least one anticancer compound. In certain preferred embodiments, the container is a container for intravenous administration. In other embodiments, the anticancer compound is

a taxane, preferably paclitaxel or docetaxel. In important embodiments, the conjugate is not encapsulated in a liposome.

According to still another aspect of the invention, methods for treating a subject having an abnormal mammalian cell proliferative disorder are provided. The methods include administering  
5 a composition including at least one fatty acid-anticancer compound conjugate to the subject in an amount which is at least about 10% greater than the maximum tolerated dose (MTD) for the unconjugated at least one anticancer compound. Preferably the amount of the at least one fatty acid-anticancer compound administered is at least about 20% greater than the MTD, 30% greater than the MTD, 40% greater than the MTD, 50% greater than the MTD, 75% greater than the MTD,  
10 100% greater than the MTD, 200% greater than the MTD, 300% greater than the MTD, or 400% greater than the MTD for the unconjugated at least one anticancer compound. In other embodiments, the anticancer compound is a taxane, preferably paclitaxel or docetaxel. In important embodiments, the conjugate is not encapsulated in a liposome.

In still another aspect of the invention, kits for administration of a fatty acid-anticancer  
15 compound conjugate composition to a subject is provided. The kits include a container containing a composition which includes at least one fatty acid-anticancer compound conjugate, and instructions for administering the at least one fatty acid-anticancer compound conjugate to subject in need of such treatment in an amount which is at least about 10% greater than the maximum tolerated dose (MTD) for the unconjugated at least one anticancer compound. Preferably the  
20 subject has an abnormal mammalian cell proliferative disorder. Preferably the amount of the at least one fatty acid-anticancer compound conjugate to be administered is at least about 20% greater than the MTD, 30% greater than the MTD, 40% greater than the MTD, 50% greater than the MTD, 75% greater than the MTD, 100% greater than the MTD, 200% greater than the MTD, 300% greater than the MTD, or 400% greater than the MTD for the unconjugated at least one anticancer  
25 compound. In certain preferred embodiments, the container is a container for intravenous administration. In other embodiments, the anticancer compound is a taxane, particularly paclitaxel or docetaxel. In important embodiments, the conjugate is not encapsulated in a liposome.

A method for increasing the therapeutic index of anticancer compounds in a subject is provided according to another aspect of the invention. The method includes conjugating a fatty  
30 acid to an anticancer compound to form a fatty acid-anticancer compound conjugate; and administering the fatty acid-anticancer compound conjugate to the subject. The therapeutic index of the anticancer compound thus administered is improved relative to non-conjugated formulations



of the anticancer compound. Preferably the subject has an abnormal mammalian cell proliferative disorder, and the subject preferably is human. In certain embodiments, the anticancer compound is a taxane, preferably paclitaxel or docetaxel. In important embodiments, the conjugate is not encapsulated in a liposome.

5 According to another aspect of the invention, methods for administering a fatty acid-anticancer compound conjugate to a subject in need of such treatment are provided. The method includes infusing the conjugate in fewer than 3 hours. Preferably the conjugate is infused in 2 hours or less. Preferably the subject has an abnormal mammalian cell proliferative disorder, and the subject preferably is human. In certain embodiments, the anticancer compound is a taxane,  
10 preferably paclitaxel or docetaxel. In important embodiments, the conjugate is not encapsulated in a liposome. In the foregoing method, it is preferred that a dose of a fatty acid-conjugated anticancer compound is administered which exceeds the maximum tolerated dose of the unconjugated anticancer compound.

According to one aspect of the invention, an injectable preparation of at least one fatty  
15 acid-taxane conjugate composition is provided. The preparation includes greater than about 6 mg/ml of the at least one fatty acid-taxane conjugate composition. Preferably, the preparation includes greater than about 7 mg/ml, 8 mg/ml, 10 mg/ml, 15 mg/ml, 20 mg/ml, 40 mg/ml, 60 mg/ml, 80 mg/ml, or 100 mg/ml of the at least one fatty acid-taxane conjugate composition. Preferred taxanes include paclitaxel and docetaxel.

20 The invention also provides an injectable composition of at least one fatty acid-taxane conjugate which includes less than about 0.3 mg/ml of the at least one fatty acid-taxane conjugate. Preferably the composition includes less than about 0.275, 0.25, 0.225, 0.2, 0.15, or 0.1 mg/ml of the at least one fatty acid-taxane conjugate. Preferred taxanes include paclitaxel and docetaxel.

According to another aspect of the invention, fatty acid-taxane conjugate compositions are  
25 provided. The compositions include an amount of at least one fatty acid-taxane conjugate greater than about 6 mg/ml. The compositions also include a surfactant. Preferably the compositions include greater than about 7 mg/ml, 8 mg/ml, 10 mg/ml, 15 mg/ml, 20 mg/ml, 40 mg/ml, 60 mg/ml, 80 mg/ml, or 100 mg/ml of the at least one fatty acid-taxane conjugate. Preferred taxanes include paclitaxel and docetaxel.

30 In certain embodiments, the surfactant in the fatty acid-taxane conjugate compositions is Cremophor EL or EL-P. Preferably the concentration of Cremophor is between about 9.6% and about 49.7% (vol/vol).

In yet another aspect of the invention, other fatty acid-taxane conjugate compositions are provided. The compositions include at least about 37 mg/ml of at least one fatty acid-taxane conjugate. Preferably, the compositions include at least about 40 mg/ml, 50 mg/ml, 60 mg/ml, 80 mg/ml, or 100 mg/ml of the at least one fatty acid-taxane conjugate. Preferably the taxane is  
5 paclitaxel or docetaxel.

According to still another aspect of the invention, fatty acid-taxane conjugate compositions are provided which have certain ratios between the amount of the fatty acid-taxane conjugates and volume of surfactant. The compositions include at least one fatty acid-taxane conjugate and a surfactant; the ratio of the weight of the at least one fatty acid-taxane conjugate and volume of the  
10 surfactant is at least about 50 mg/ml. Preferably the ratio of the weight of the at least one fatty acid-taxane conjugate and volume of the surfactant is at least about 60 mg/ml, 70 mg/ml, 80 mg/ml, 90 mg/ml, or 100 mg/ml. The preferred surfactants include Cremophor EL and EL-P, and the preferred taxanes include paclitaxel or docetaxel. In other embodiments, the compositions include a solvent, preferably ethanol; the preferred ratio of surfactant to solvent is about 1:1.

15 In still another aspect of the inventions, fatty acid-taxane conjugate compositions are provided which have certain ratios between the amount of the fatty acid-taxane conjugate and volume of solvent. The compositions include at least one fatty acid-taxane conjugate and a solvent; the ratio of the weight of the at least one fatty acid-taxane conjugate and volume of the solvent is at least about 42 mg/ml. Preferably the ratio of the weight of the at least one fatty acid-  
20 taxane conjugate and volume of the solvent is at least about 50 mg/ml, 60 mg/ml, 70 mg/ml, 80 mg/ml, 90 mg/ml, or 100 mg/ml. The preferred solvents include ethanol, and the preferred taxanes include paclitaxel or docetaxel. In other embodiments, the compositions include a surfactant, preferably Cremophor EL or EL-P; the preferred ratio of surfactant to solvent is about 1:1.

According to another aspect of the invention, compositions of fatty acid-taxane conjugates  
25 which include solvent and surfactant are provided. The compositions include between about 7 and about 120 milligrams of a fatty acid-taxane conjugate, between about 40% and 100% of solvent, and between about 1% and about 60% surfactant. In preferred embodiments, the compositions include between about 20 mg and about 120 mg of a fatty acid-taxane conjugate, between about 40% and 100% of solvent, and between about 1% and about 60% surfactant. More preferably,  
30 compositions include between about 35 mg and about 45 milligrams of a fatty acid-taxane conjugate, between about 45% and about 55% of solvent, and between about 45% and about 55% surfactant. In particularly preferred embodiments, the compositions include between about 6 mg

and about 20 milligrams of a fatty acid-taxane conjugate, between about 5% and about 15% of solvent, and between about 5% and about 15% surfactant, or between about 6 mg and about 12 milligrams of a fatty acid-taxane conjugate, between about 8% and about 12% of solvent, and between about 8% and about 12% surfactant, or between about 1 mg and about 5 milligrams of  
5 a fatty acid-taxane conjugate, between about 1% and about 10% of solvent, and between about 0.5% and about 4% surfactant. Preferably the solvent is ethanol and the surfactant is Cremophor EL or EL-P.

For all of the foregoing, the fatty acid is preferably a C8-C26 fatty acid. More preferably, the fatty acid is a C8-C26 unbranched, naturally occurring fatty acid. More preferably, the fatty  
10 acid is selected from the group consisting of C8:0 (caprylic acid), C10:0 (capric acid), C12:0 (lauric acid), C14:0 (myristic acid), C16:0 (palmitic acid), C16:1 (palmitoleic acid), C16:2, C18:0 (stearic acid), C18:1 (oleic acid), C18:1-7 (vaccenic), C18:2-6 (linoleic acid), C18:3-3 ( $\alpha$ -linolenic acid), C18:3-5 (eleostearic), C18:3-6 ( $\beta$ -linolenic acid), C18:4-3, C20:1 (gondoic acid), C20:2-6, C20:3-6 (dihomo- $\gamma$ -linolenic acid), C20:4-3, C20:4-6 (arachidonic acid), C20:5-3  
15 (eicosapentaenoic acid), C22:1 (docosenoic acid), C22:4-6 (docosatetraenoic acid), C22:5-6 (docosapentaenoic acid), C22:5-3 (docosapentaenoic), C22:6-3 (docosahexaenoic acid) and C24:1-9 (nervonic). Particularly preferred is docosahexaenoic acid.

In the foregoing compositions, products and methods, ranges of doses, ratios, and amounts have been given. The ranges include the numbers specifically set forth as well as each and every  
20 number therebetween. Thus, for example, when an amount of a fatty acid-taxane conjugate is specified as "greater than about 6 mg/ml, 7 mg/ml, 8 mg/ml, 10 mg/ml, 15 mg/ml, 20 mg/ml, 40 mg/ml, 60 mg/ml, 80 mg/ml, 100 mg/ml," the range includes conjugates in the amounts of 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, and so on including each number throughout the range.

25 According to yet another aspect of the invention, a method for treating a subject having an abnormal mammalian proliferative disorder is provided. The method involves administering to the subject a fatty acid-taxane conjugate in an amount of the conjugate which is at least 250, 275, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1050, 1100, 1150, 1200, 1250, 1300, 1350 or 1400 mg/meter<sup>2</sup> of body surface area (BSA). In one embodiment, the  
30 amount is administered to the subject over a period of 24 hours or less, 6 hours or less, 3 hours or less, or 2 hours or less. In some embodiments, the fatty acid is a C8-C26 fatty acid. In important embodiments, the fatty acid is a C16-C22 unbranched, naturally occurring fatty acid. In certain

particularly preferred embodiments, the fatty acid can be linoleic acid, palmitic acid, arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid, 2-octanoate, 2-hexanoate, CH<sub>3</sub>-hexanoate, CH<sub>3</sub>-butanoate, or oleic acid. In the most preferred embodiments, the fatty acid is linoleic acid, palmitic acid, arachidonic acid, eicosapentaenoic acid, or docosahexaenoic acid. In preferred embodiments, the taxane is paclitaxel. In important embodiments, when the taxane is paclitaxel, the fatty acid is conjugated at the 2' OH position of paclitaxel. In the most preferred embodiment, the fatty acid is docosahexaenoic acid.

In any of the foregoing embodiments, the Maximum Tolerated Dose can be determined according to procedures known to those of ordinary skill in the art. The Maximum Tolerated Doses of many compounds are already known. Some for known anti-cancer agents are listed below.

According to another aspect of the invention, a composition of matter is provided. The composition comprises a crystal of a conjugate of a polyunsaturated C16-26 fatty acid and a drug. In preferred embodiments, the fatty acid is a C16-C22 fatty acid. In some embodiments the fatty acid is a naturally-occurring, unbranched fatty acid. In certain embodiments, the fatty acid can be linoleic acid, palmitic acid, arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid, 2-octanoate, 2-hexanoate, CH<sub>3</sub>-hexanoate, CH<sub>3</sub>-butanoate, or oleic acid. In particularly preferred embodiments, the fatty acid is linoleic acid, palmitic acid, arachidonic acid, eicosapentaenoic acid, or docosahexaenoic acid. The polymorph of the crystal of docosahexaenoic acid-paclitaxel is described in the examples.

In any of the foregoing embodiments, the drug can be among those listed below. The drug must contain a site (reactive group) amenable for conjugation to a fatty acid. Chemists of ordinary skill in the art can make such determinations. Preferred categories of drugs are anti-cancer agents, anti-viral agents and anti-psychotic agents. The anti-cancer compound can be a taxane. In certain embodiments, the taxane is paclitaxel. In important embodiments, when the taxane is paclitaxel, the fatty acid is conjugated at the 2' OH position of paclitaxel. In particularly preferred embodiments, the fatty acid is docosahexaenoic acid.

According to a further aspect of the invention, a method for isolating a conjugate of a polyunsaturated C16-C22 fatty acid and a drug is provided. The method involves covalently conjugating the fatty acid and the drug to form the conjugate, forming a crystal of the conjugate, and isolating the crystal. In some embodiments, the fatty acid is an oil at room temperature. The preferred fatty acids, drugs, anticancer compounds, and conjugates are as described above.

-11-

According to another aspect of the invention, a kit is provided. The kit comprises a package containing a first container housing a solution of a conjugate of a fatty acid and a taxane dissolved in a first solvent, a second container causing a mixture of a second solvent and a surfactant, the second solvent miscible with the first solvent, and instructions for combining the solution and the mixture. In one embodiment, the first solvent is ethanol. In certain embodiments, the surfactant is cremophor. In further embodiments, the second solvent is ethanol. In important embodiments, the cremophor is present in a ratio to the second solvent of at least 1:1, 2:1, 3:1, or 4:1. The preferred fatty acids, anticancer compounds, and conjugates are as described above. In particularly preferred embodiments, the concentration of the conjugate in the solvent is about 100 mg/ml.

According to still another aspect of the invention, a pharmaceutical preparation is provided. The pharmaceutical preparation comprises an intravenous solution of a conjugate of a C8-C26 fatty acid and a taxane, wherein the solution is substantially free of liposomes. Preferred fatty acids, anticancer compounds, and conjugates are as described above.

According to a further aspect of the invention, a method for preparing an intravenous solution for administration to a subject having a mammalian cell proliferative disorder, is provided. The method involves combining (a) a solution of a conjugate of a fatty acid and a taxane dissolved in a first solvent, and (b) a mixture of a second solvent and a surfactant, the second solvent miscible with the first solvent, and said combining resulting in a pre-mix, and adding the pre-mix to an intravenous solution. In one embodiment, the first solvent is an alcohol, preferably ethanol. In certain embodiments, the surfactant is cremophor. In further embodiments, the second solvent is an alcohol, preferably ethanol. In important embodiments, the cremophor is present in a ratio to the second solvent of at least 1:1, 2:1, 3:1, or 4:1. The preferred fatty acids, anticancer compounds, and conjugates are as described above. In particularly preferred embodiments, the concentration of the conjugate in the solvent is about 100 mg/ml.

These and other aspects of the invention, as well as various advantages and utilities, will be more apparent with reference to the detailed description of the preferred embodiments.

### **Brief Description of the Drawings**

Figure 1 depicts a kit 11 comprising packaging 15, a first agent of the invention 17 (e.g., a container that contains *TAXOPREXIN*<sup>®</sup> CONCENTRATE [“Concentrate”]), a second agent of the invention 19 (e.g., a container that contains DILUENT FOR *Taxoprexin*<sup>®</sup> Concentrate

["*Diluent*"]), and instructions 21, for utilizing such agents in therapeutic applications.

### **Detailed Description of the Invention**

*Cis*-docosahexaenoic acid (DHA) is a naturally occurring fatty acid. It is an unbranched  
5 chain fatty acid with six double bonds, all *cis*. Its structure is as follows:



DHA can be isolated, for example, from fish oil or can be chemically synthesized. These  
10 methods, however, can generate *trans* isomers, which are difficult and expensive to separate and which may present safety problems in humans. The preferred method of production is biological synthesis to produce the all *cis* isomer. The preferred source of DHA is from Martek Biosciences Corporation of Columbia, Maryland. Martek has a patented system for manufacturing DHA using microalgae which synthesize only a single isomer of DHA, the all *cis* isomer. Martek's patents  
15 include U.S. Pat. Nos. 5,374,657, 5,492,938, 5,407,957 and 5,397,591.

DHA also is present in the milk of lactating women, and Martek's licensee has obtained approval in Europe of DHA as a nutritional supplement for infant formula.

It is known that DHA can be unstable in the presence of oxygen. To stabilize DHA and its conjugates it is important to add anti-oxidants to the material after it is synthesized. One  
20 method of stabilization is to make-up the newly synthesized material in the following solution: 100 g neat DHA-paclitaxel plus 100 g of vehicle (100ml propylene glycol, 70 mg  $\alpha$ -tocopherol, 5 mg dialaurylthiodipropionic acid, 50 mg ascorbic acid) prepared and held under argon in amber, sealed vials and stored at four degrees centigrade. The following anti-oxidants may also be employed: ascorbic acid, ascorbyl palmitate, dilauryl ascorbate, hydroquinone, butyated  
25 hydroxyanisole, sodium meta bisulfite, *t*-B carotene and  $\alpha$ -tocopherol. A heavy metal chelator such as ethylenediamine tetra-acetic acid (EDTA) may also be used.

Paclitaxel was first isolated from the bark of *Taxus brevifolia* (Wani et al., J. Am. Chem. Soc., 93, 2325, 1971). Its isolation and synthesis have been reported extensively in the literature. Applicants obtained paclitaxel from a commercial source, Hauser Laboratories, of Boulder,  
30 Colorado.

The preferred compound of the invention, "Taxoprexin<sup>TM</sup>", is a covalent conjugate of DHA and paclitaxel. Its chemical structure, synthesis, purification and *in vitro* action are described in U.S Patent 5,795,909, the entire disclosure of which is incorporated by reference herein. The structure is shown as "conjugate 1" in Example 1 of that patent.

5       The maximum tolerated dose (MTD) for any therapeutic compound is identified as part of its clinical evaluation. For example, phase I trials can include a determination of the maximum tolerated dose, dose limiting toxicities (DLT) and pharmacokinetics of a test compound. "Maximum tolerated dose," as used herein, refers to the largest dose of a pharmaceutical agent that an adult patient can take with safety to treat a particular disease or condition. Thus, the MTD for  
10       any Food and Drug Administration (FDA) approved therapeutic compound is known to those of ordinary skill in the art as a matter of the public record. The MTD for any particular therapeutic compound may vary according to its formulation (e.g., injectable formulation, implantable bioerodible polymer formulation, oral formulation), route of delivery (e.g., intravenous, oral, intratumoral), manner of delivery (e.g., infusion, bolus injection), dosing schedule (e.g., hourly, daily, weekly) and the like. The MTD frequently is defined as the highest dose level at which 50%  
15       of subjects administered with the drug develop a dose limiting toxicity. The doses for anti-neoplastic pharmaceutical agents found in the Physicians Desk Reference (PDR) are defined as the MTD for those agents. The MTD is further defined to include only doses for drugs (including anti-neoplastics) used as single agents and without additional cellular, genetic, pharmaceutical, or  
20       other agents added to alter the MTD. Other definitions which are clinically relevant and generally accepted will be known to one of ordinary skill in the art.

Measurement of maximum tolerated dose may be expressed as weight of drug per weight of subject, weight of drug per body surface area, etc. The MTD of anticancer compounds is frequently expressed as weight per square meters (mg/m<sup>2</sup>) of body surface area. For example, the  
25       MTD for paclitaxel infusion in humans is 225 mg/m<sup>2</sup>. The most often used clinical tolerated dose is 175 mg/m<sup>2</sup>. MTD also may be expressed as a dose relative to a time component, such as weight of drug per body surface area per day.

For therapeutics which have not yet been subjected to human clinical trials, or subjected to any determination of the MTD in humans (e.g., experimental or highly toxic compounds), one  
30       of skill in the art can estimate the MTD by using animal models. Calculation of MTD in animals may be based on a number of physiological parameters, such as death, particular toxicities, drug induced weight loss. Using death as an endpoint, the MTD may be the dose given test animals in

-14-

which each member of the test group survived. Using toxicity as an endpoint, the MTD may be the dose at which moderate but not severe toxicity is observed. Using weight loss as an endpoint, the MTD may be the dose above which a certain percent change in body weight is induced. Other methods for determining MTDs using animal models and various endpoints are known to one of  
5 ordinary skill in the art. Correlation of animal MTDs to human MTDs for a therapeutic compound is an accepted practice in the pharmaceutical arts.

For example, it has been determined that a conjugate of DHA and paclitaxel (Taxoprexin™) has a maximum tolerated dose in animals (mice, rats and dogs) which is about 4-5 times greater (by weight) than paclitaxel alone or about 3-4 times greater (by molarity) than  
10 paclitaxel alone.

The invention in another aspect provides compositions and formulations for administration to a subject, preferably a human subject, containing amounts of a fatty acid-anticancer compound conjugate which exceeds the maximum tolerated dose for the unconjugated anticancer compound. The fatty acid-anticancer compound conjugate preferably is in a container for administration to  
15 a subject. Preferably the container is a container for intravenous administration, such as an IV bag.

The amount of the fatty acid-anticancer compound in the container is at least about 10% greater than the MTD for the unconjugated compound. Preferably the amount of the fatty acid-anticancer compound in the container is at least about 20%, 30%, 40%, 50%, 75%, 100%, 200%, 300% or 400% greater than the MTD for the unconjugated at least one anticancer compound. The  
20 anticancer compound is preferably a taxane, particularly paclitaxel or docetaxel.

Methods for administering these compositions to subjects having an abnormal mammalian cell proliferative disorder also are provided.

Kits containing fatty acid-anticancer compounds in amounts also are provided. The kits contain one or more containers with the conjugated anticancer compound along with instructions  
25 for mixing, diluting and/or administering the anticancer compound in amounts greater than the MTD for the unconjugated anticancer compound. The kits also can include other containers with one or more solvents, surfactants, preservatives and/or diluents (e.g. normal saline (0.9% NaCl), or 5% dextrose (D5W)), as well as containers for mixing, diluting, and/or administering the conjugates to a subject in need of such treatment. A kit embodying features of the present  
30 invention, generally designated by the numeral 11, is illustrated in Figure 1. Kit 11 is comprised of the following major elements: packaging 15, a first agent of the invention 17 (e.g., a container that contains *TAXOPREXIN*® CONCENTRATE [“Concentrate”]), a second agent of the invention



19 (e.g., a container that contains DILUENT FOR *Taxoprexin*<sup>®</sup> Concentrate [*"Diluent"*]), and instructions 21 for utilizing such agents in therapeutic applications. Individuals skilled in the art can readily modify packaging 15 to suit individual needs.

The anticancer compounds in the kit may be provided as liquid solutions, or as dried  
5 powders. When the compound provided is a dry powder, the powder may be reconstituted by the addition of a suitable solvent, which also may be provided. Liquid forms of the conjugates may be concentrated (for dilution prior to administration) or ready to administer to a subject. The solvent will depend on the drug and the mode of administration. Suitable solvents are well known for known drug compounds and are available in the literature.

10 As noted above, the therapeutic index is the ratio of the median toxic dose to the median effective dose. Conjugation of fatty acids to anticancer compounds to form a fatty acid-anticancer compound conjugate reduces toxicity of the anticancer compounds, and increases effectiveness as compared to the unconjugated anticancer compounds. Therefore the invention also provides methods for increasing the therapeutic index of anticancer compounds in a subject. The methods  
15 include conjugating a fatty acid to an anticancer compound to form a fatty acid-anticancer compound conjugate and administering the fatty acid-anticancer compound conjugate to the subject. The therapeutic index of the anticancer compound conjugate is improved relative to unconjugated formulations of the anticancer compound. Preferably the anticancer compound is a taxane, particularly paclitaxel or docetaxel.

20 Although the conjugate may be encapsulated in a liposome, it is preferred that the conjugate is not encapsulated by a liposome. The preferred subjects for the method are humans.

The conjugated anticancer compounds described herein are less toxic and more effective than the corresponding unconjugated anticancer compounds. Therefore the fatty acid-anticancer compound conjugates can be administered in amounts which are equally toxic but more effective,  
25 or in doses which are equally effective and less toxic than the corresponding unconjugated anticancer compounds. In general, conjugation of fatty acids to anticancer compounds permits an increase in the maximum tolerated dose relative to unconjugated anticancer compounds.

The invention provides injectable preparations of at least one fatty acid-taxane conjugate composition. The injectable preparations are prepared for administration to a subject in need of  
30 treatment with a taxane, e.g., a subject having cancer. The injectable preparations contain higher concentrations of taxane derivatives than was previously thought possible. For example, present infusion formulations of paclitaxel contain 0.3 mg/ml - 1.2 mg/ml diluted in aqueous solution. It

has been found, surprisingly, that taxane derivatives having a conjugated fatty acid, as disclosed herein, can be administered at much higher concentrations to subjects without the dose limiting toxicities observed with other taxane formulations. The injectable preparations have greater than about 6 mg/ml of the fatty acid-taxane conjugates described herein. Preferably, the preparations  
5 contain greater than about 7 mg/ml, greater than about 8 mg/ml, greater than about 9 mg/ml, greater than about 10 mg/ml, greater than about 12 mg/ml, and so on.

In addition, low-dose injectable preparations of taxanes having lower amounts of taxanes than the formulations presently used clinically are also provided. The surprisingly increased activity of fatty acid-taxane conjugates relative to unconjugated taxanes permits administration of  
10 lesser amounts while obtaining the same anticancer activity. Thus, injectable preparations having less than 0.3 mg/ml are provided, which formulations have anticancer activity when administered to a subject with cancer. Preferably the low-dose injectable preparations contain less than about 0.25 mg/ml, less than about 0.2 mg/ml, less than about 0.15 mg/ml, less than about 0.1 mg/ml, and so on.

Other compositions are provided which have still higher amounts of fatty acid-taxane conjugates. In some embodiments, the compositions contain greater than about 6 mg/ml of at least one fatty acid-taxane conjugate and a surfactant. Preferably, the compositions contain greater than about 7 mg/ml, greater than about 8 mg/ml, greater than about 9 mg/ml, greater than about 10 mg/ml, greater than about 12 mg/ml, and so on. In other embodiments, the compositions include  
20 at least about 37 mg/ml of at least one fatty acid-taxane conjugate. Preferably such compositions contain at least about 40 mg/ml, at least about 50 mg/ml, at least about 60 mg/ml, at least about 80 mg/ml, and at least about 100 mg/ml of at least one fatty acid-taxane conjugate.

The foregoing preparations, formulations and compositions may be encapsulated by liposomes, according to standard procedures for preparation of liposomes, but preferably are not.

25 All of the compositions herein which contain taxanes or other anticancer compounds optionally can contain additional anticancer compounds. The compositions also can contain other components useful in formulating anticancer compounds for administration to humans, including surfactants, solvents, preservatives, diluents, and the like, all of which are standard in the pharmaceutical arts.

30 Suitable surfactants for use with the present invention include nonionic agents, such as long-chain fatty acids and their water-insoluble derivatives. These include fatty alcohols such as lauryl cetyl and stearyl alcohol, glyceryl esters such as the naturally occurring mono-, di- and

triglycerides, and fatty acid esters of fatty alcohols, such as propylene glycol, polyethylene glycol, sorbitan, sucrose and cholesterol. Also useful are compounds that are those that have polyoxyethylene groups added through an ether linkage with an alcohol group. Compounds that are particularly useful in the present invention include the polyoxyethylene sorbitan fatty acid esters and polyoxyethylene glycerol and steroidal esters. Particularly preferred surfactants are Cremophor® EL and Cremophor® EL-P, which are polyoxyethylated castor oil surfactants.

It is contemplated that other surfactants may be used to solubilize the compositions described herein. For example, it is contemplated that polysorbate 80, polysorbate 20, sodium laurate, sodium oleate, and sorbitan monooleate may be useful in context of the present invention. Anionic surfactants may also be useful in the practice of the present invention. Examples of these include, but are not limited to, sodium cholate, sodium lauryl sulfate, sodium deoxycholate, sodium laurate, sodium oleate, and potassium laurate.

In certain embodiments, dehydrated ethanol is used as a solvent for the compositions described herein. In other embodiments, glycols such as propylene glycol or polyethylene glycol are within the scope of the invention. Simple complex polyols may also be suitable solvents. Moreover, the use of non-dehydrated alcohols may also be suitable within the scope of the present invention. It is recognized that the determination of a solvent and its proper concentration to fully solubilize the fatty acid-anticancer compositions is within the scope of a skilled artisan, and would not require undue experimentation.

For example, a conjugate of DHA and paclitaxel (Taxoprexin™) can be supplied at 100mg/ml in EtOH. The concentrated conjugate can be diluted 2:3 with a 4:1 Cremophor EL:EtOH surfactant/solvent mixture, resulting in an intermediate solution of 40 mg/ml DHA-paclitaxel in a Cremophor/ EtOH vehicle. This intermediate solution can be diluted 1:5 into an injection vehicle such as normal saline 5% dextrose to give a final composition of 8 mg/ml DHA-paclitaxel in Cremophor/EtOH.

DHA and other naturally occurring, unbranched fatty acids may be conjugated to virtually any anti-cancer compound and used according to the methods of the present invention. Those of ordinary skill in the art will recognize also numerous other compounds that fall within the categories and that are useful according to the invention.

Anti-cancer compounds include, but are not limited to, the following compounds and classes of compounds:

Antineoplastic agents such as: Acivicin; Aclarubicin; Acodazole Hydrochloride; Acronine; Adozelesin; Adriamycin; Aldesleukin; Altretamine; Ambomycin; Ametantrone Acetate; Aminoglutethimide; Amsacrine; Anastrozole; Anthramycin; Asparaginase; Asperlin; Azacitidine; Azetepa; Azotomycin; Batimastat; Benzodepa; Bicalutamide; Bisantrone Hydrochloride; Bisnafide

5 Dimesylate; Bizelesin; Bleomycin Sulfate; Brequinar Sodium; Bropiramine; Busulfan; Cactinomycin; Calusterone; Caracemide; Carbetimer; Carboplatin; Carmustine; Carubicin Hydrochloride; Carzelesin; Cedefingol; Chlorambucil; Cirolemycin; Cisplatin; Cladribine; Crisnatol Mesylate; Cyclophosphamide; Cytarabine; Dacarbazine; DACA (N-[2-(Dimethyl-amino)ethyl]acridine-4-carboxamide); Dactinomycin; Daunorubicin Hydrochloride; Daunomycin;

10 Decitabine; Dexormaplatin; Dezaguanine; Dezaguanine Mesylate; Diaziquone; Docetaxel; Doxorubicin; Doxorubicin Hydrochloride; Droloxifene; Droloxifene Citrate; Dromostanolone Propionate; Duazomycin; Edatrexate; Eflornithine Hydrochloride; Elsamitrucin; Enloplatin; Enpromate; Epiropidine; Epirubicin Hydrochloride; Erbulozole; Esorubicin Hydrochloride; Estramustine; Estramustine Phosphate Sodium; Etanidazole; Ethiodized Oil I 131; Etoposide;

15 Etoposide Phosphate; Etoprine; Fadrozole Hydrochloride; Fazarabine; Fenretinide; Floxuridine; Fludarabine Phosphate; Fluorouracil; 5-FdUMP; Flurocitabine; Fosquidone; Fostriecin Sodium; Gemcitabine; Gemcitabine Hydrochloride; Gold Au 198; Hydroxyurea; Idarubicin Hydrochloride; Ifosfamide; Ilmofofosine; Interferon Alfa-2a; Interferon Alfa-2b; Interferon Alfa-n1; Interferon Alfa-n3; Interferon Beta- I a; Interferon Gamma- I b; Iproplatin; Irinotecan Hydrochloride; Lanreotide

20 Acetate; Letrozole; Leuprolide Acetate; Liarozole Hydrochloride; Lometrexol Sodium; Lomustine; Losoxantrone Hydrochloride; Masoprocol; Maytansine; Mechlorethamine Hydrochloride; Megestrol Acetate; Melengestrol Acetate; Melphalan; Menogaril; Mercaptopurine; Methotrexate; Methotrexate Sodium; Metoprine; Meturedopa; Mitindomide; Mitocarcin; Mitocromin; Mitogillin; Mitomalcin; Mitomycin; Mitosper; Mitotane; Mitoxantrone Hydrochloride; Mycophenolic Acid;

25 Nocodazole; Nogalamycin; Ormaplatin; Oxisuran; Paclitaxel; Pegaspargase; Peliomycin; Pentamustine; Peplomycin Sulfate; Perfosfamide; Pipobroman; Pipo sulfan; Piroxantrone Hydrochloride; Plicamycin; Plomestane; Porfimer Sodium; Porfiromycin; Prednimustine; Procarbazine Hydrochloride; Puromycin; Puromycin Hydrochloride; Pyrazofurin; Riboprine; Rogletimide; Safingol; Safingol Hydrochloride; Semustine; Simtrazene; Sparfosate Sodium;

30 Sparsomycin; Spirogermanium Hydrochloride; Spiromustine; Spiroplatin; Streptonigrin; Streptozocin; Strontium Chloride Sr 89; Sulofenur; Talisomycin; Taxane; Taxoid; Tecogalan Sodium; Tegafur; Teloxantrone Hydrochloride; Temoporfin; Teniposide; Teroxirone;

Testolactone; Thiamiprine; Thioguanine; Thiotepa; Thymitaq; Tiazofurin; Tirapazamine; Tomudex; TOP-53; Topotecan Hydrochloride; Toremifene Citrate; Trestolone Acetate; Triciribine Phosphate; Trimetrexate; Trimetrexate Glucuronate; Triptorelin; Tubulozole Hydrochloride; Uracil Mustard; Uredepa; Vapreotide; Verteporfin; Vinblastine; Vinblastine Sulfate; Vincristine; 5 Vincristine Sulfate; Vindesine; Vindesine Sulfate; Vinepidine Sulfate; Vinglycinate Sulfate; Vinleurosine Sulfate; Vinorelbine Tartrate; Vinrosidine Sulfate; Vinzolidine Sulfate; Vorozole; Zeniplatin; Zinostatin; Zorubicin Hydrochloride; 2-Chlorodeoxyadenosine; 2'-Deoxyformycin; 9-aminocamptothecin; raltitrexed; N-propargyl-5,8-dideazafolic acid; 2-chloro-2'-arabino-fluoro-2'-deoxyadenosine; 2-chloro-2'-deoxyadenosine; anisomycin; trichostatin A; hPRL-G129R; CEP-10 751; linomide; sulfur mustard; nitrogen mustard (mechlorethamine); cyclophosphamide; melphalan; chlorambucil; ifosfamide; busulfan; N-methyl-N-nitrosourea (MNU); N, N'-Bis(2-chloroethyl)-N-nitrosourea (BCNU); N-(2-chloroethyl)-N'-cyclohexyl-N-nitrosourea (CCNU); N-(2-chloroethyl)-N'-(trans-4-methylcyclohexyl)-N-nitrosourea (MeCCNU); N-(2-chloroethyl)-N'-(diethyl)ethylphosphonate-N-nitrosourea (fotemustine); streptozotocin; diacarbazine (DTIC); 15 mitozolomide; temozolomide; thiotepa; mitomycin C; AZQ; adozelesin; Cisplatin; Carboplatin; Ormaplatin; Oxaliplatin; C1-973; DWA 2114R; JM216; JM335; Bis (platinum); tomudex; azacitidine; cytarabine; gemcitabine; 6-Mercaptopurine; 6-Thioguanine; Hypoxanthine; teniposide 9-amino camptothecin; Topotecan; CPT-11; Doxorubicin; Daunomycin; Epirubicin; darubicin; mitoxantrone; losoxantrone; Dactinomycin (Actinomycin D); amsacrine; pyrazoloacridine; all-20 trans retinol; 14-hydroxy-retro-retinol; all-trans retinoic acid; N-(4-Hydroxyphenyl) retinamide; 13-cis retinoic acid; 3-Methyl TTNEB; 9-cis retinoic acid; fludarabine (2-F-ara-AMP); 2-chlorodeoxyadenosine (2-Cda).

Other anti-neoplastic compounds include: 20-epi-1,25 dihydroxyvitamin D<sub>3</sub>; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; 25 ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; 30 arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstauroporine; beta lactam derivatives; beta-alethine;

betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine;  
 bisnafide; bistratene A; bizelesin; breflata; bleomycin A<sub>2</sub>; bleomycin B<sub>2</sub>; bropirimine; budotitane;  
 buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives (e.g., 10-hydroxy-  
 camptothecin); canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole;  
 5 CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS);  
 castanospermine; cecropin B; cetorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost;  
 cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B;  
 combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin  
 8; cryptophycin A derivatives; curacin A; cyclopentantraquinones; cycloplatan; cypemycin;  
 10 cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B;  
 2'-deoxycoformycin (DCF); deslorelin; dexifosfamide; dexrazoxane; dexverapamil; diaziquone;  
 didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin;  
 diphenyl spiromustine; discodermolide; docosanol; dolasetron; doxifluridine; droloxifene;  
 dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine;  
 15 elemene; emitefur; epirubicin; epothilones (A, R = H; B, R = Mc); epithilones; epristeride;  
 estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide; etoposide  
 4'-phosphate (etopofos); exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride;  
 flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorubicin hydrochloride; forfenimex;  
 formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine;  
 20 ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin;  
 hexamethylene bisacetamide; homoharringtonine (HHT); hypericin; ibandronic acid; idarubicin;  
 idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant  
 peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons;  
 interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; irinotecan; iroplact; irsogladine;  
 25 isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N  
 triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia  
 inhibiting factor; leukocyte alpha interferon; leuprolide + estrogen + progesterone; leuprorelin;  
 levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic  
 platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine;  
 30 losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides;  
 maitansine; mannostatin A; marimastat; masoprocil; maspin; matrilysin inhibitors; matrix  
 metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide;

MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA;  
 mithracin; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth  
 factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic  
 gonadotrophin; monophosphoryl lipid A + myobacterium cell wall sk; mopidamol; multiple drug  
 5 resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent;  
 mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted  
 benzamides; nafarelin; nagrestip; naloxone + pentazocine; napavin; naphterpin; nartograstim;  
 nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric  
 oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone;  
 10 oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer;  
 ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel analogues; paclitaxel derivatives;  
 palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin;  
 pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentroze;  
 perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors;  
 15 picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen  
 activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex;  
 podophyllotoxin; porfimer sodium; porfiromycin; propyl bis-acridone; prostaglandin J2;  
 proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein  
 kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside  
 20 phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene  
 conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras  
 inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin;  
 ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1;  
 ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine;  
 25 senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal  
 transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium  
 borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic  
 acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor;  
 stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive  
 30 intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans;  
 tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur;  
 tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide;

tetrachlorodecaoxide; tetrazomine; thaliblastinc; thalidomide; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene dichloride; topotecan; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; 5 tricitabine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer.

10 Antiproliferative agent: Piritrexim Isothionate.

Antiprostatic hypertrophy: Sitogluside.

Benign prostatic hyperplasia therapy agent: Tamsulosin Hydrochloride.

Prostate growth inhibitor: Pentomone.

Radioactive agents: Fibrinogen I 125; Fludeoxyglucose F 18; Fluorodopa F 18; Insulin I 125; Insulin I 131; Iobenguane I 123; Iodipamide Sodium I 131; Iodoantipyrine I 131; Iodocholesterol I 131; Iodohippurate Sodium I 123; Iodohippurate Sodium I 125; Iodohippurate Sodium I 131; Iodopyracet I 125; Iodopyracet I 131; Iofetamine Hydrochloride I 123; Iomethin I 125; Iomethin I 131; Iothalamate Sodium I 125; Iothalamate Sodium I 131; Iotyrosine I 131; Liothyronine I 125; Liothyronine I 131; Merisoprol Acetate Hg 197; Merisoprol Acetate Hg 203; 20 Merisoprol Hg 197; Selenomethionine Se 75; Technetium Tc 99m Antimony Trisulfide Colloid; Technetium Tc 99m Bicisate; Technetium Tc 99m Disofenin; Technetium Tc 99m Etidronate; Technetium Tc 99m Exametazime; Technetium Tc 99m Furifosmin; Technetium Tc 99m Gluceptate; Technetium Tc 99m Lidofenin; Technetium Tc 99m Mebrofenin; Technetium Tc 99m Medronate; Technetium Tc 99m Medronate Disodium; Technetium Tc 99m Mertiatide; 25 Technetium Tc 99m Oxidronate; Technetium Tc 99m Pentetate; Technetium Tc 99m Pentetate Calcium Trisodium; Technetium Tc 99m Sestamibi; Technetium Tc 99m Siboroxime; Technetium Tc 99m Succimer; Technetium Tc 99m Sulfur Colloid; Technetium Tc 99m Teboroxime; Technetium Tc 99m Tetrafosmin; Technetium Tc 99m Tiatide; Thyroxine I 125; Thyroxine I 131; Tolpovidone I 131; Triolein I 125; Triolein I 131.

30 Anti-cancer Supplementary Potentiating Agents: Tricyclic anti-depressant drugs (e.g., imipramine, desipramine, amitriptyline, clomipramine, trimipramine, doxepin, nortriptyline, protriptyline, amoxapine and maprotiline); non-tricyclic anti-depressant drugs (e.g., sertraline,



trazodone and citalopram);  $\text{Ca}^{++}$  antagonists (e.g., verapamil, nifedipine, nitrendipine and caroverine); Calmodulin inhibitors (e.g., prenylamine, trifluoroperazine and clomipramine); Amphotericin B; Triparanol analogues (e.g., tamoxifen); antiarrhythmic drugs (e.g., quinidine); antihypertensive drugs (e.g., reserpine); Thiol depleters (e.g., buthionine and sulfoximine) and  
5 Multiple Drug Resistance reducing agents such as Cremaphor EL. The compounds of the invention also can be administered with cytokines such as granulocyte colony stimulating factor.

Preferred anticancer agents (some with their MTDs shown in parentheses) include: gemcitabine (1000 mg/m<sup>2</sup>); methotrexate (15 gm/m<sup>2</sup> i.v.+ leuco. <500 mg/m<sup>2</sup> i.v. w/o leuco); 5-FU (500 mg/m<sup>2</sup>/day x 5days); FUDR (100 mg/kg x 5 in mice, 0.6 mg/kg/day in human i.a.); FdUMP;  
10 Hydroxyurca (35 mg/kg/d in man); Docetaxel (60-100 mg/m<sup>2</sup>); discodermolide; epothilones; vincristine (1.4 mg/m<sup>2</sup>); vinblastine (escalating: 3.3 - 11.1 mg/m<sup>2</sup>, or rarely to 18.5 mg/m<sup>2</sup>); vinorelbine (30 mg/m<sup>2</sup>/wk); meta-pac; irinotecan (50-150 mg/m<sup>2</sup>, 1 x /wk depending on patient response); SN-38 (~100 times more potent than Irinotecan); 10-OH campto; topotecan (1.5 mg/m<sup>2</sup>/day in humans, 1 x iv LD10mice=75 mg/m<sup>2</sup>); etoposide (100 mg/m<sup>2</sup> in man); adriamycin;  
15 flavopiridol; Cis-Pt (100mg/m<sup>2</sup> in man); carbo-Pt (360 mg/m<sup>2</sup> in man); bleomycin (20 mg/m<sup>2</sup>); mitomycin C (20 mg/m<sup>2</sup>); mithramycin (30 µg/kg); capecitabine (2.5 g/m<sup>2</sup> orally); cytarabine (100 mg/m<sup>2</sup>/day); 2-Cl-2'-deoxyadenosine; Fludarabine-PO<sub>4</sub> (25 mg/m<sup>2</sup>/day, x 5days); mitoxantrone (12-14 mg/m<sup>2</sup>); mitozolomide (>400 mg/m<sup>2</sup>); Pentostatin; Tomudex.

As used herein, a taxane is a molecule that possesses a tricyclic carbon-atom connectivity  
20 network, which may incorporate carbon-carbon multiple bonds, and which through the involvement of carbon-atom-noncarbon-atom bonds may include substituents, functional groups, and additional rings. The structure of taxanes, as used herein, is shown in U.S. patent 5,795,909.

A taxoid is a molecule structurally related to a taxane in which the above taxane carbon-atom connectivity network is altered, for example, by cleavage of one or more of the carbocyclic  
25 rings, by deletion or addition of carbon substituents, by connection of carbon atoms normally not bonded to each other, by disconnection of carbon atoms normally bonded to each other, or by some other reorganization of or adjustment to the taxane carbon-atom connectivity network, but in which one or more structural features characteristic of the taxane carbon-atom connectivity network are conserved.

30 The compounds useful in the invention may be delivered in the form of anti-cancer cocktails. An anti-cancer cocktail is a mixture of any one of the compounds useful with this invention with another anti-cancer agent such as an anti-cancer drug, a cytokine, and/or

supplementary potentiating agent(s). The use of cocktails in the treatment of cancer is routine. In this embodiment, a common administration vehicle (e.g., pill, tablet, implant, injectable solution, etc.) would contain both the conjugate useful in this invention and the anti-cancer drug and/or supplementary potentiating agent.

5       The anti-cancer conjugates of the invention also are useful, in general, for treating mammalian cell proliferative disorders other than cancer, including psoriasis, actinic keratosis, etc. They further are useful in treating diabetes and its complications, excess acid secretion, cardiovascular conditions involving cholesterol (e.g., hyperlipidemia and hypercholesterolemia), diarrhea, ovarian diseases (e.g. endometriosis, ovarian cysts, etc.) and as contraceptive agents.

10       In another aspect the invention provides additional compositions of matter. Compositions according to this aspect of the invention comprise substantially pure crystals of a conjugate of a fatty acid and a drug. In this aspect of the invention, the fatty acids are polyunsaturated fatty acids. In some embodiments, the fatty acid is preferably a C16-C26 unbranched, naturally occurring fatty acid. The fatty acid can be selected from the group consisting of C8:0 (caprylic acid), C10:0 (capric acid), C12:0 (lauric acid), C14:0 (myristic acid), C16:0 (palmitic acid), C16:1 (palmitoleic acid), C16:2, C18:0 (stearic acid), C18:1 (oleic acid), C18:1-7 (vaccenic), C18:2-6 (linoleic acid), C18:3-3 ( $\alpha$ -linolenic acid), C18:3-5 (eleostearic), C18:3-6 ( $\beta$ -linolenic acid), C18:4-3, C20:1 (gondoic acid), C20:2-6, C20:3-6 (dihomo- $\gamma$ -linolenic acid), C20:4-3, C20:4-6 (arachidonic acid), C20:5-3 (eicosapentaenoic acid), C22:1 (docosenoic acid), C22:4-6 (docosatetraenoic acid), C22:5-6 (docosapentaenoic acid), C22:5-3 (docosapentaenoic ), C22:6-3 (docosahexaenoic acid) and C24:1-9 (nervonic). Particularly preferred is docosahexaenoic acid. In certain embodiments, the fatty acid can be linoleic acid, palmitic acid, arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid, 2-octanoate, 2-hexanoate, CH<sub>3</sub>-hexanoate, CH<sub>3</sub>-butanoate, or oleic acid. In particularly preferred embodiments, the fatty acid is linoleic acid, palmitic acid, arachidonic acid, eicosapentaenoic acid, or docosahexaenoic acid.

25       The drug according to this aspect of the invention can be any drug that can form a conjugate with a fatty acid. Preferably, the drug has free groups reactive with a free acid of the fatty acid. More preferably, the drug has a free -OH or -NH<sub>2</sub> group. Drugs include, but are not limited to, the following agents: adrenergic agent; adrenocortical steroid; adrenocortical suppressant; alcohol deterrent; aldosterone antagonist; amino acid; ammonia detoxicant; anabolic; analeptic; analgesic; androgen; anesthesia, adjunct to; anesthetic; anorectic; antagonist; anterior pituitary suppressant; anthelmintic; anti-acne agent; anti-adrenergic; anti-allergic;

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anti-amebic; anti-androgen; anti-anemic; anti-anginal; anti-anxiety; anti-arthritic; anti-asthmatic; anti-atherosclerotic; antibacterial; anticholelithic; anticholelithogenic; anticholinergic; anticoagulant; anticoccidal; anticonvulsant; antidepressant; antidiabetic; antidiarrheal; antidiuretic; antidote; anti-emetic; anti-epileptic; anti-estrogen; antifibrinolytic; antifungal; 5 antiglaucoma agent; antihemophilic; antihemorrhagic; antihistamine; antihyperlipidemia; antihyperlipoproteinemic; antihypertensive; antihypotensive; anti-infective; anti-infective, topical; anti-inflammatory; antikeratinizing agent; antimalarial; antimicrobial; antimigraine; antimitotic; antimycotic, antinauseant, antineoplastic, antineutropenic, antiobsessional agent; antiparasitic; antiparkinsonian; antiperistaltic, antipneumocystic; antiproliferative; antiprostatic 10 hypertrophy; antiprotozoal; antipruritic; antipsychotic; antirheumatic; antischistosomal; antiseborrheic; antisecretory; antispasmodic; antithrombotic; antitussive; anti-ulcerative; anti-urolithic; antiviral; appetite suppressant; benign prostatic hyperplasia therapy agent; blood glucose regulator; bone resorption inhibitor; bronchodilator; carbonic anhydrase inhibitor; cardiac depressant; cardioprotectant; cardiostimulant; cardiovascular agent; choleric; cholinergic; cholinergic 15 agonist; cholinesterase deactivator; coccidiostat; cognition adjuvant; cognition enhancer; depressant; diagnostic aid; diuretic; dopaminergic agent; ectoparasiticide; emetic; enzyme inhibitor; estrogen; fibrinolytic; fluorescent agent; free oxygen radical scavenger; gastrointestinal motility effector; glucocorticoid; gonad-stimulating principle; hair growth stimulant; hemostatic; histamine H2 receptor antagonists; hormone; hypocholesterolemic; hypoglycemic; hypolipidemic; 20 hypotensive; imaging agent; immunizing agent; immunomodulator; immunoregulator; immunostimulant; immunosuppressant; impotence therapy adjunct; inhibitor; keratolytic; LNRH agonist; liver disorder treatment; luteolysin; memory adjuvant; mental performance enhancer; mood regulator; mucolytic; mucosal protective agent; mydriatic; nasal decongestant; neuromuscular blocking agent; neuroprotective; NMDA antagonist; non-hormonal sterol 25 derivative; oxytocic; plasminogen activator; platelet activating factor antagonist; platelet aggregation inhibitor; post-stroke and post-head trauma treatment; potentiator; progestin; prostaglandin; prostate growth inhibitor; prothyrotropin; psychotropic; pulmonary surface; radioactive agent; regulator; relaxant; repartitioning agent; scabicide; sclerosing agent; sedative; sedative-hypnotic; selective adenosine A1 antagonist; serotonin antagonist; serotonin inhibitor; 30 serotonin receptor antagonist; steroid; stimulant; suppressant; symptomatic multiple sclerosis; synergist; thyroid hormone; thyroid inhibitor; thyromimetic; tranquilizer; treatment of amyotrophic lateral sclerosis; treatment of cerebral ischemia; treatment of Paget's disease; treatment of unstable

angina; uricosuric; vasoconstrictor; vasodilator; vulnerary; wound healing agent; xanthine oxidase inhibitor.

Lists of compounds in each of these categories can be found in U.S. Patent 5,795,909, the disclosure of which is incorporated herein by reference. Among preferred groups of drugs are anti-cancer agents, anti-infectives including anti-bacterials and anti-virals, and neurological agents including anti-psychotics. Anti-cancer agents and preferred anti-cancer agents are as described above.

Anti-infectives include Difloxacin Hydrochloride; Lauryl Isoquinolinium Bromide; Moxalactam Disodium; Ornidazole; Pentisomicin; Sarafloxacin Hydrochloride; Protease inhibitors of HIV and other retroviruses; Integrase Inhibitors of HIV and other retroviruses; Cefaclor (Ceclor); Acyclovir (Zovirax); Norfloxacin (Noroxin); Cefoxitin (Mefoxin); Cefuroxime axetil (Ceftin); Ciprofloxacin (Cipro); Aminacrine Hydrochloride; Benzethonium Chloride : Bithionolate Sodium; Bromchlorenone; Carbamide Peroxide; Cetalkonium Chloride; Cetylpyridinium Chloride : Chlorhexidine Hydrochloride; Clioquinol; Domiphen Bromide; Fenticlor; Fludazonium Chloride; Fuchsin, Basic; Furazolidone; Gentian Violet; Halquinols; Hexachlorophene : Hydrogen Peroxide; Ichthammol; Imidecyl Iodine; Iodine; Isopropyl Alcohol; Mafenide Acetate; Meralein Sodium; Mercufenol Chloride; Mercury, Ammoniated; Methylbenzethonium Chloride; Nitrofurazone; Nitromersol; Octenidine Hydrochloride; Oxychlorosene; Oxychlorosene Sodium; Parachlorophenol, Camphorated; Potassium Permanganate; Povidone-Iodine; Sepazonium Chloride; Silver Nitrate; Sulfadiazine, Silver; Symclosene; Thimerfonate Sodium; Thimerosal; Troclosene Potassium.

Anti-bacterials include: Acedapsone; Acetosulfone Sodium; Alamecin; Alexidine; Amdinocillin; Amdinocillin Pivoxil; Amicycline; Amifloxacin; Amifloxacin Mesylate; Amikacin; Amikacin Sulfate; Aminosalicyclic acid; Aminosalicylate sodium; Amoxicillin; Amphomycin; Ampicillin; Ampicillin Sodium; Apalcillin Sodium; Apramycin; Aspartocin; Astromicin Sulfate; Avilamycin; Avoparcin; Azithromycin; Azlocillin; Azlocillin Sodium; Bacampicillin Hydrochloride; Bacitracin; Bacitracin Methylene Disalicylate; Bacitracin Zinc; Bambermycins; Benzoylpas Calcium; Berythromycin; Betamicin Sulfate; Biapenem; Biniramycin; Biphenamine Hydrochloride; Bispyrithione Magsulfex; Butikacin; Butirosin Sulfate; Capreomycin Sulfate; Carbadox; Carbenicillin Disodium; Carbenicillin Indanyl Sodium; Carbenicillin Phenyl Sodium; Carbenicillin Potassium; Carumonam Sodium; Cefaclor; Cefadroxil; Cefamandole; Cefamandole Nafate; Cefamandole Sodium; Cefaparole; Cefatrizine; Cefazaflur Sodium; Cefazolin; Cefazolin

Sodium; Cefbuperazone; Cefdinir; Cefepime; Cefepime Hydrochloride; Cefetecol; Cefixime; Cefmenoxime Hydrochloride; Cefmetazole; Cefmetazole Sodium; Cefonicid Monosodium; Cefonicid Sodium; Cefoperazone Sodium; Ceforanide; Cefotaxime Sodium; Cefotetan; Cefotetan Disodium; Cefotiam Hydrochloride; Cefoxitin; Cefoxitin Sodium; Cefpimizole; Cefpimizole Sodium; Cefpiramide; Cefpiramide Sodium; Cefpirome Sulfate; Cefpodoxime Proxetil; Cefprozil; Cefroxadine; Cefsulodin Sodium; Ceftazidime; Ceftibuten; Ceftizoxime Sodium; Ceftriaxone Sodium; Cefuroxime; Cefuroxime Axetil; Cefuroxime Pivoxetil; Cefuroxime Sodium; Cephacetrile Sodium; Cephalixin; Cephalixin Hydrochloride; Cephaloglycin; Cephaloridine; Cephalothin Sodium; Cephapirin Sodium; Cephradine; Cetocycline Hydrochloride; Cetophenicol; Chloramphenicol; Chloramphenicol Palmitate; Chloramphenicol Pantothenate Complex; Chloramphenicol Sodium Succinate; Chlorhexidine Phosphanilate; Chloroxylonol; Chlortetracycline Bisulfate; Chlortetracycline Hydrochloride; Cinoxacin; Ciprofloxacin; Ciprofloxacin Hydrochloride; Cirolemycin; Clarithromycin; Clinafloxacin Hydrochloride; Clindamycin; Clindamycin Hydrochloride; Clindamycin Palmitate Hydrochloride; Clindamycin Phosphate; Clofazimine; Cloxacillin Benzathine; Cloxacillin Sodium; Cloxyquin; Colistimethate Sodium; Colistin Sulfate; Coumermycin; Coumermycin Sodium; Cyclacillin; Cycloserine; Dalfopristin; Dapsone; Daptomycin; Demeclocycline; Demeclocycline Hydrochloride; Demecycline; Denofungin; Diaveridine; Dicloxacillin; Dicloxacillin Sodium; Dihydrostreptomycin Sulfate; Dipyrithione; Dirithromycin; Doxycycline; Doxycycline Calcium; Doxycycline Fosfatex; Doxycycline Hyclate; Droxacin Sodium; Enoxacin; Epicillin; Eritetracycline Hydrochloride; Erythromycin; Erythromycin Acistrate; Erythromycin Estolate; Erythromycin Ethylsuccinate; Erythromycin Gluceptate; Erythromycin Lactobionate; Erythromycin Propionate; Erythromycin Stearate; Ethambutol Hydrochloride; Ethionamide; Fleroxacin; Floxacillin; Fludalanine; Flumequine; Fosfomycin; Fosfomycin Tromethamine; Fumoxicillin; Furazolium Chloride; Furazolium Tartrate; Fusidate Sodium; Fusidic Acid; Gentamicin Sulfate; Gloximonam; Gramicidin; Haloproglin; Hetacillin; Hetacillin Potassium; Hexedine; Ibafoxacin; Imipenem; Isoconazole; Isepamicin; Isoniazid; Josamycin; Kanamycin Sulfate; Kitasamycin; Levofuraltadone; Levopropylcillin Potassium; Lexithromycin; Lincomycin; Lincomycin Hydrochloride; Lomefloxacin; Lomefloxacin Hydrochloride; Lomefloxacin Mesylate; Loracarbef; Mafenide; Meclocycline; Meclocycline Sulfosalicylate; Megalomycin Potassium Phosphate; Mequidox; Meropenem; Methacycline; Methacycline Hydrochloride; Methenamine; Methenamine Hippurate; Methenamine Mandelate; Methicillin Sodium; Metioprime;

Metronidazole Hydrochloride; Metronidazole Phosphate; Mezlocillin; Mezlocillin Sodium; Minocycline; Minocycline Hydrochloride; Mirincamycin Hydrochloride; Monensin; Monensin Sodium; Nafcillin Sodium; Nalidixate Sodium; Nalidixic Acid; Natamycin; Nebramycin; Neomycin Palmitate; Neomycin Sulfate; Neomycin Undecylenate; Netilmicin Sulfate; 5 Neutramycin; Nifuradene; Nifuraldezone; Nifuratel; Nifuratrone; Nifurdazil; Nifurimide; Nifurpirinol; Nifurquinazol; Nifurthiazole; Nitrocyline; Nitrofurantoin; Nitromide; Norfloxacin; Novobiocin Sodium; Ofloxacin; Ormetoprim; Oxacillin Sodium; Oximonam; Oximonam Sodium; Oxolinic Acid; Oxytetracycline; Oxytetracycline Calcium; Oxytetracycline Hydrochloride; Paldimycin; Parachlorophenol; Paulomycin; Pefloxacin; Pefloxacin Mesylate; Penamecillin; 10 Penicillin G Benzathine; Penicillin G Potassium; Penicillin G Procaine; Penicillin G Sodium; Penicillin V; Penicillin V Benzathine; Penicillin V Hydrabamine; Penicillin V Potassium; Pentizidone Sodium; Phenyl Aminosaliclate; Piperacillin Sodium; Pirbenicillin Sodium; Piridicillin Sodium; Pirlimycin Hydrochloride; Pivampicillin Hydrochloride; Pivampicillin Pamoate; Pivampicillin Probenate; Polymyxin B Sulfate; Porfiromycin; Propikacin; Pyrazinamide; 15 Pyrithione Zinc; Quindecamine Acetate; Quinupristin; Racephenicol; Ramoplanin; Ranimycin; Relomycin; Repromycin; Rifabutin; Rifametan; Rifamexil; Rifamide; Rifampin; Rifapentine; Rifaximin; Rolitetracycline; Rolitetracycline Nitrate; Rosaramicin; Rosaramicin Butyrate; Rosaramicin Propionate; Rosaramicin Sodium Phosphate; Rosaramicin Stearate; Rosoxacin; Roxarsone; Roxithromycin; Sancycline; Sanfetrinem Sodium; Sarmoxicillin; Sarpicillin; 20 Scopafungin; Sisomicin; Sisomicin Sulfate; Sparfloxacin; Spectinomycin Hydrochloride; Spiramycin; Stallimycin Hydrochloride; Steffimycin; Streptomycin Sulfate; Streptonicozid; Sulfabenz; Sulfabenzamide; Sulfacetamide; Sulfacetamide Sodium; Sulfacytine; Sulfadiazine; Sulfadiazine Sodium; Sulfadoxine; Sulfalene; Sulfamerazine; Sulfameter; Sulfamethazine; Sulfamethizole; Sulfamethoxazole; Sulfamonomethoxine; Sulfamoxole; Sulfanilate Zinc; 25 Sulfantran; Sulfasalazine; Sulfasomizole; Sulfathiazole; Sulfazamet; Sulfisoxazole; Sulfisoxazole Acetyl; Sulfisoxazole Diolamine; Sulfomyxin; Sulopenem; Sultamicillin; Suncillin Sodium; Talampicillin Hydrochloride; Teicoplanin; Terafloxacin Hydrochloride; Temocillin; Tetracycline; Tetracycline Hydrochloride; Tetracycline Phosphate Complex; Tetroxoprim; Thiamphenicol; Thiphencillin Potassium; Ticarcillin Cresyl Sodium; Ticarcillin Disodium; Ticarcillin 30 Monosodium; Ticlatone; Tiodonium Chloride; Tobramycin; Tobramycin Sulfate; Tosufloxacin; Trimethoprim; Trimethoprim Sulfate; Trisulfapyrimidines; Troleandomycin; Trospectomycin Sulfate; Tyrothricin; Vancomycin; Vancomycin Hydrochloride; Virginiamycin; Zorbamycin.

Anti-virals include: Acemannan; Acyclovir; Acyclovir Sodium; Adefovir; Alovudine; Alvircept Sudotox; Amantadine Hydrochloride; Aranotin; Arildone; Atevirdine Mesylate; Avridine; Cidofovir; Cipamfylline; Cytarabine Hydrochloride; Delavirdine Mesylate; Desciclovir; Didanosine; Disoxaril; Edoxudine; Enviroxime; Famciclovir; Famotidine Hydrochloride; Fiacitabine; Fialuridine; Fosarilate; Foscarnet Sodium; Fosfonet Sodium; Ganciclovir; Ganciclovir Sodium; Idoxuridine; Kethoxal; Lamivudine; Lobucavir; Memotidine Hydrochloride; Methisazone; Nevirapine; Penciclovir; Pirodavir; Ribavirin; Rimantadine Hydrochloride; Saquinavir Mesylate; Somantadine Hydrochloride; Sorivudine; Statolon; Stavudine; Tilorone Hydrochloride; Trifluridine; Valacyclovir Hydrochloride; Vidarabine; Vidarabine Phosphate; Vidarabine Sodium Phosphate; Viroxime; Zalcitabine; Zidovudine; Ziniviroxime and integrase inhibitors.

Neurological agents, including anti-psychotics, include, but are not limited to: Acetophenazine Maleate; Alentemol Hydrobromide; Alpertine; Azaperone; Batelapine Maleate; Benperidol; Benzindopyrine Hydrochloride; Brofoxine; Bromperidol; Bromperidol Decanoate; Butaclamol Hydrochloride; Butaperazine; Butaperazine Maleate; Carphenazine Maleate; Carvotroline Hydrochloride; Chlorpromazine; Chlorpromazine Hydrochloride; Chlorprothixene; Cinperene; Cintriamide; Clomacran Phosphate; Clopenthixol; Clopimozide; Clopipazan Mesylate; Cloroperone Hydrochloride; Clothiapine; Clothixamide Maleate; Clozapine; Cyclophenazine Hydrochloride; Droperidol; Etazolate Hydrochloride; Fenimide; Flucindole; Flumezapine; Fluphenazine Decanoate; Fluphenazine Enanthate; Fluphenazine Hydrochloride; Fluspiperone; Fluspirilene; Flutroline; Gevotroline Hydrochloride; Halopemide; Haloperidol; Haloperidol Decanoate; Iloperidone; Imidoline Hydrochloride; Lenperone; Mazapertine Succinate; Mesoridazine; Mesoridazine Besylate; Metiapine; Milenperone; Milipertine; Molindone Hydrochloride; Naranol Hydrochloride; Neflumozide Hydrochloride; Ocaperidone; Olanzapine; Oxiperomide; Penfluridol; Pentiapine Maleate; Perphenazine; Pimozide; Pinoxepin Hydrochloride; Pipamperone; Piperacetazine; Pipotiazine Palmitate; Piquindone Hydrochloride; Prochlorperazine Edisylate; Prochlorperazine Maleate; Promazine Hydrochloride; Remoxipride; Remoxipride Hydrochloride; Rimcazole Hydrochloride; Seperidol Hydrochloride; Sertindole; Setoperone; Spiperone; Thioridazine; Thioridazine Hydrochloride; Thiothixene; Thiothixene Hydrochloride; Tioperidone Hydrochloride; Tiospirone Hydrochloride; Trifluoperazine Hydrochloride; Trifluoperidol; Triflupromazine; Triflupromazine Hydrochloride; Ziprasidone Hydrochloride; Benztropine Mesylate; Biperiden; Biperiden Hydrochloride; Biperiden Lactate; Carmantadine;

Ciladopa Hydrochloride; Dopamantine; Ethopropazine Hydrochloride; Lazabemide; Levodopa; Lometraline Hydrochloride; Mofegiline Hydrochloride; Naxagolide Hydrochloride; Pareptide Sulfate; Procyclidine Hydrochloride; Quinelorane Hydrochloride; Ropinirole Hydrochloride; Selegiline Hydrochloride; Tolcapone; Trihexyphenidyl Hydrochloride; Felbamate; Loreclezole; 5 Tolgabide; Adatanserin Hydrochloride; Adinazolam; Adinazolam Mesylate; Alaproclate; Aletamine Hydrochloride; Amedalin Hydrochloride; Amitriptyline Hydrochloride; Amoxapine; Aptazapine Maleate; Azaloxan Fumarate; Azepindole; Azipramine Hydrochloride; Bipenamol Hydrochloride; Bupropion Hydrochloride; Butacetin; Butriptyline Hydrochloride; Caroxazone; Cartazolate; Ciclazindol; Cidoxepin Hydrochloride; Cilobamine Mesylate; Clodazon 10 Hydrochloride; Clomipramine Hydrochloride; Cotinine Fumarate; Cyclindole; Cypenamine Hydrochloride; Cyprolidol Hydrochloride; Cyproximide; Daledalin Tosylate; Dapoxetine Hydrochloride; Dazadrol Maleate; Dazepinil Hydrochloride; Desipramine Hydrochloride; Dexamisole; Deximafen; Dibenzepin Hydrochloride; Dioxadrol Hydrochloride; Dothiepin Hydrochloride; Doxepin Hydrochloride; Duloxetine Hydrochloride; Eclanamine Maleate; 15 Encyprate; Etoperidone Hydrochloride; Fantridone Hydrochloride; Fenmetozole Hydrochloride; Fenmetramide; Fezolamine Fumarate; Fluotracen Hydrochloride; Fluoxetine; Fluoxetine Hydrochloride; Fluparoxan Hydrochloride; Gamfexine; Guanoxyfen Sulfate; Imafen Hydrochloride; Imiloxan Hydrochloride; Imipramine Hydrochloride; Indeloxazine Hydrochloride; Intriptyline Hydrochloride; Iprindole; Isocarboxazid; Ketipramine Fumarate; Lofepramine 20 Hydrochloride; Lortalamine; Maprotiline; Maprotiline Hydrochloride; Melitracen Hydrochloride; Milacemide Hydrochloride; Minaprine Hydrochloride; Mirtazapine; Moclobemide; Modaline Sulfate; Napactadine Hydrochloride; Napamezole Hydrochloride; Nefazodone Hydrochloride; Nisoxetine; Nitrafudam Hydrochloride; Nomifensine Maleate; Nortriptyline Hydrochloride; Octriptyline Phosphate; Opipramol Hydrochloride; Oxaprotiline Hydrochloride; Oxypertine; 25 Paroxetine; Phenelzine Sulfate; Pirandamine Hydrochloride; Pizotiline; Pridefine Hydrochloride; Prolintane Hydrochloride; Protriptyline Hydrochloride; Quipazine Maleate; Rolicyprine; Seroxetine Hydrochloride; Sertraline Hydrochloride; Sibutramine Hydrochloride; Sulpiride; Suritozole; Tametraline Hydrochloride; Tampramine Fumarate; Tandamine Hydrochloride; Thiazesim Hydrochloride; Thozalinone; Tomoxetine Hydrochloride; Trazodone Hydrochloride; 30 Trebenzomine Hydrochloride; Trimipramine; Trimipramine Maleate; Venlafaxine Hydrochloride; Viloxazine Hydrochloride; Zimeldine Hydrochloride; Zometapine; Albutoin; Ameltolide; Atolide; Buramate; Carbamazepine; Cinromide; Citenamide; Clonazepam; Cyheptamide; Dezinamide;



Dimethadione; Divalproex Sodium; Eterobarb; Ethosuximide; Ethotoin; Flurazepam Hydrochloride; Fluzinamide; Fosphenytoin Sodium; Gabapentin; Ilicpicamide; Lamotrigine; Magnesium Sulfate; Mephentoin; Mephobarbital; Methetoin; Methsuximide; Milacemide Hydrochloride; Nabazenil; Nafimidone Hydrochloride; Nitrazepam; Phenacemide; Phenobarbital; 5 Phenobarbital Sodium; Phensuximide; Phenytoin; Phenytoin Sodium; Primidone; Progabide; Ralitoline; Remacemide Hydrochloride; Ropizine; Sabeluzole; Stiripentol; Sulthiame; Thiopental Sodium; Tiletamine Hydrochloride; Topiramate; Trimethadione; Valproate Sodium; Valproic Acid; Vigabatrin; Zoniclezole Hydrochloride; Zonisamide; Alverinc Citrate; Anisotropine Methylbromide; Atropine; Atropine Oxide Hydrochloride; Atropine Sulfate; Belladonna; 10 Benapryzine Hydrochloride; Benzetimide Hydrochloride; Benzilium Bromide; Biperiden; Biperiden Hydrochloride; Biperiden Lactate; Clidinium Bromide; Cyclopentolate Hydrochloride; Dextemide; Dicyclomine Hydrochloride; Dihexyverine Hydrochloride; Domazoline Fumarate; Elantrine; Elucaine; Ethybenztropine; Eucatropine Hydrochloride; Glycopyrrolate; Heteronium Bromide; Homatropine Hydrobromide; Homatropine Methylbromide; Hyoscyamine; 15 Hyoscyamine Hydrobromide; Hyoscyamine Sulfate; Isopropamide Iodide; Mepenzolate Bromide; Methylatropine Nitrate; Metoquinine; Oxybutynin Chloride; Parapenzolate Bromide; Pentapiperium Methylsulfate; Phencarbamide; Poldine Methylsulfate; Proglumide; Propantheline Bromide; Propenzolate Hydrochloride; Scopolamine Hydrobromide; Tematropium Methylsulfate; Tiqinamide Hydrochloride; Tofenacin Hydrochloride; Toquinine; Triampyzine Sulfate; 20 Trihexyphenidyl Hydrochloride; Tropicamide.

Preferred antipsychotics include: Lorazepam; chlordiazepoxide; clorazepate; diazepam; alprazolam; hydroxyzine; buspirone; venlafaxine; mephobarbital; meprobamate; doxepin; perphenazine; hydroxyzine pamoate; venlafaxine; mirtazapine; nefazodone; bupropion; phenelzine; tranlycypromine; citalopram; paraxefine; sertraline; amitriptyline; protriptyline; 25 divalproex; clonazepam; clozapine; haloperidol; loxapine; molindone; thiothixene; pimozide; risperidone; quefiapine; thiothixen; olanzapine; quetiapine; prochlorperazine; mesoridazin; trifluoperazine; chlorpromazine; perphenazine; fluvoxamine. Most preferred antipsychotics include: clozapine; venlafaxine; risperidone; quefiapine; thiothixen; olanzapine.

The compounds of the invention, when used alone or in cocktails, are administered in 30 therapeutically effective amounts. A therapeutically effective amount will be determined by the parameters discussed below; but, in any event, is that amount which establishes a level of the drug(s) in the area of the tumor which is effective in inhibiting the tumor growth.

When administered, the formulations of the invention are applied in pharmaceutically acceptable amounts and in pharmaceutically acceptable compositions. Such preparations may routinely contain salts, buffering agents, preservatives, compatible carriers, and optionally other therapeutic ingredients. When used in medicine the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically acceptable salts thereof and are not excluded from the scope of the invention. Such pharmacologically and pharmaceutically acceptable salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, acetic, salicylic, p-toluene sulfonic, tartaric, citric, methane sulfonic, formic, malonic, succinic, naphthalene-2-sulfonic, and benzene sulfonic. Also, pharmaceutically acceptable salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts.

Suitable buffering agents include: acetic acid and a salt (1-2% W/V); citric acid and a salt (1-3% W/V); boric acid and a salt (0.5-2.5% W/V); and phosphoric acid and a salt (0.8-2% W/V).

Suitable preservatives include benzalkonium chloride (0.003-0.03% W/V); chlorobutanol (0.3-0.9% W/V); parabens (0.01-0.25% W/V) and thimerosal (0.004-0.02% W/V).

The active compounds of the present invention may be a pharmaceutical composition having a therapeutically effective amount of a conjugate of the invention optionally included in a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier" as used herein means one or more compatible solid or liquid filler, dilutants or encapsulating substances which are suitable for administration to a human or other animal. The term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions are capable of being commingled with the molecules of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficacy.

Compositions suitable for parenteral administration conveniently comprise a sterile preparation of the conjugates of the invention. This preparation may be formulated according to known methods. Formulations for taxanes can be found in Chapter 9 of Taxol: Science and Applications, CRC Press, Inc., 2000 Corporate Boulevard, N.W., Boca Raton, FL 33431. In general, Taxol has been formulated as a 6 mg/ml Cremophor EL® (polyoxyethylated castor oil)/ethanol mixture, which is diluted to final volume with normal saline or 5% dextrose. A

15mg/ml solution of Taxotere has been formulated in polysorbate 80 (polyoxyethylene sorbitanmonooleate)/ethanol mixture, diluted with 5% dextrose. This is in contrast to the formulations described herein.

The sterile preparation thus may be a sterile solution or suspension in a non-toxic parenterally-acceptable diluent or solvent. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono or di-glycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables. Carrier formulations suitable for oral, subcutaneous, intravenous, intramuscular, etc. can be found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA.

A subject as used herein means humans, primates, horses, cows, pigs, sheep, goats, dogs, cats and rodents.

The conjugates of the invention are administered in effective amounts. An effective amount means that amount necessary to delay the onset of, inhibit the progression of, halt altogether the onset or progression of or diagnose the particular condition being treated. In general, an effective amount for treating cancer will be that amount necessary to inhibit mammalian cancer cell proliferation in-situ. When administered to a subject, effective amounts will depend, of course, on the particular condition being treated; the severity of the condition; individual patient parameters including age, physical condition, size and weight; concurrent treatment; frequency of treatment; and the mode of administration. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is preferred generally that a maximum dose be used, that is, the highest safe dose according to sound medical judgment.

Dosage may be adjusted appropriately to achieve desired drug levels, locally or systemically. Generally, daily oral doses of active compounds will be from about 0.01 mg/kg per day to 1000 mg/kg per day. It is expected that IV doses in the range of about 1 to 1000 mg/m<sup>2</sup> per day will be effective. In the event that the response in a subject is insufficient at such doses, even higher doses (or effective higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. Continuous IV dosing over, for example 24 hours or multiple doses per day are contemplated to achieve appropriate systemic levels of compounds. Preferred dosing schedules, including concentration, length of administration, and the like are described herein elsewhere (see Examples).

A variety of administration routes are available. The particular mode selected will depend of course, upon the particular drug selected, the severity of the disease state being treated and the dosage required for therapeutic efficacy. The methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that  
5 produces effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, sublingual, topical, nasal, transdermal, intradermal or parenteral routes. The term "parenteral" includes subcutaneous, intravenous, intramuscular, or infusion. Intravenous routes are preferred for taxanes.

The compositions may conveniently be presented in unit dosage form and may be prepared  
10 by any of the methods well known in the art of pharmacy. All methods include the step of bringing the conjugates of the invention into association with a carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing the compounds into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product.

15 Compositions suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of the active compound. Other compositions include suspensions in aqueous liquors or non-aqueous liquids such as a syrup, an elixir, or an emulsion.

Other delivery systems can include time-release, delayed release or sustained release  
20 delivery systems. Such systems can avoid repeated administrations of the active compounds of the invention, increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer based systems such as polylactic and polyglycolic acid, polyanhydrides and polycaprolactone; nonpolymer systems that are lipids including sterols such as cholesterol,  
25 cholesterol esters and fatty acids or neutral fats such as mono-, di and triglycerides; hydrogel release systems; silastic systems; peptide based systems; wax coatings, compressed tablets using conventional binders and excipients, partially fused implants and the like. In addition, a pump-based hardware delivery system can be used, some of which are adapted for implantation.

A long-term sustained release implant also may be used. "Long-term" release, as used  
30 herein, means that the implant is constructed and arranged to deliver therapeutic levels of the active ingredient for at least 30 days, and preferably 60 days. Long-term sustained release implants are well known to those of ordinary skill in the art and include some of the release

-35-

systems described above. Such implants can be particularly useful in treating solid tumors by placing the implant near or directly within the tumor, thereby affecting localized, high-doses of the compounds of the invention.

The invention will be more fully understood by reference to the following examples.

5 These examples, however, are merely intended to illustrate the embodiments of the invention and are not to be construed to limit the scope of the invention.

### Examples

#### Materials and Methods

##### 10 Crystallization of DHA-Paclitaxel

As mentioned elsewhere in this application, the preferred compound of the invention, "Taxoprexin™", is a covalent conjugate of DHA and paclitaxel. Its chemical structure, synthesis, purification and *in vitro* action are described in U.S. Patent 5,795,909, the entire disclosure of which is incorporated by reference herein. In addition, a crystalline form of this conjugate was  
15 obtained using the following protocol:

The weight (W) of the chromatographically purified DNA-paclitaxel conjugate (obtained as described in U.S. Patent 5,795,909) is recorded. The amount of ethanol required for the crystallization of the chromatographically purified DNA-paclitaxel conjugate is calculated using the following equation:

20 
$$\text{mL of ethanol (E)} = \text{g of DHA-paclitaxel (W)} \times 5 \text{ to } 8 \text{ (preferably } 8)$$

Approximately  $\frac{3}{4}$  of ethanol volume (E) are added to a round bottom Erlenmeyer flask containing the DHA-paclitaxel and a stir-bar. The Erlenmeyer flask is placed on a stir-plate. The contents are stirred at room temperature or warmed to no more than 40°C while the remaining  $\frac{1}{4}$  of ethanol volume is added. If all the DHA-paclitaxel does not dissolve with the originally added  
25 ethanol volume (E), additional ethanol could be added in increments, until a clear solution is formed. The total amount of ethanol used, however, is recorded (EFin). The amount of water required for the crystallization is calculated using the following equation:

$$\text{mL of water} = \text{mL of ethanol (EFin)} \times 0.5 \text{ to } 1.5$$

The volume of water as calculated above is measured and added dropwise to the ethanol  
30 solution in the Erlenmeyer flask. Stirring is continued during the entire addition period. Even after the complete addition of the water, stirring is continued. The entire Erlenmeyer flask, including its mouth, are then covered with aluminum foil. Stirring is continued at room

temperature for at least 4 hours. The crystallization start, stop and total crystallization times are recorded. If after 4-18 hours of stirring, crystal growth is not present, the Erlenmeyer flask may be placed in the refrigerator or a cold room for at least 24 hours.

The contents of the Erlenmeyer flask are then filtered through a Buchner funnel equipped with a filter paper to an appropriately sized filter flask under vacuum (through a vacuum pump). Once the content of the Erlenmeyer flask ("mother liquor") is passed through to the clean flask, the vacuum is disrupted, and the mother liquor is transferred back into the Erlenmeyer flask. The mother liquor in the Erlenmeyer flask is swirled to rinse out any remaining crystals sticking on the sides of the flask and is again filtered under vacuum through the Buchner funnel containing the crystals from the first pass. Once the mother liquor is passed through the Buchner funnel for the second time, the crystals collected (in the filter of the funnel) are washed once with ice-cold ethanol (ethanol which has been previously placed at a below -15 °C temperature for at least 1 hour), and washed once with ice-cold hexane (hexane previously placed at a below -15 °C temperature for at least 1 hour). With the aid of a spatula and a power addition funnel, the crystals from the Buchner funnel are scraped out into a clean flask. The entire flask is covered with aluminum foil and is placed under high vacuum to dry the crystals for at least 24 hours. These crystals are then used as the source of a pure DHA-paclitaxel formulation.

DHA-paclitaxel crystallizes in the monoclinic space group  $P2_1$  (systematic absences  $0k0: k=\text{odd}$ ) with  $a=18.6418(2)\text{\AA}$ ,  $b=17.8806(4)\text{\AA}$ ,  $c=18.9812(3)\text{\AA}$ ,  $\beta=90.3920(10)^\circ$ ,  $V=6326.8(2)\text{\AA}^3$ ,  $Z=4$  (there are two molecules in the asymmetric unit) and  $d_{\text{calc}}=1.222\text{ g/cm}^3$ .

DHA-paclitaxel: The active ingredient of *Taxoprexin*<sup>®</sup>

Component	Molecular Weight	% of DHA-paclitaxel
DHA	328	27%
Paclitaxel	854	73%
DHA-paclitaxel	1164	100%

#### Animal Subject Experiments: Examples 1-7

##### Example 1: the effects of taxoprexin and paclitaxel against M 109 lung carcinoma in mice.

Syngeneic mice were injected with mouse lung tumor line M (Madison) 109 subcutaneously in the flank. Four days after tumor implantation, when the tumor weighed about 30 mg, taxoprexin (OD=120mg/kg/day x 5 days) or paclitaxel (OD=20mg/kg/day x 5 days) were injected as a bolus through the tail vein on each of five successive days (days 4 through 8). Both

-37-

drugs were dissolved in 10% cremophor EL/10% ethanol/80% saline. Tumor volume was estimated from tumor width and length. The results show that paclitaxel retarded tumor growth for about four days. In contrast, taxoprexin completely eliminated all measurable tumors in eight out of eight mice.

5 Example 2: the effects of taxoprexin and paclitaxel against M 109 lung carcinoma in mice.

Syngeneic mice were injected with mouse lung tumor line M (Madison) 109 sub-cutaneously in the flank. Five days after tumor implantation, one day later than in the last example, when the tumors had grown ten-fold larger to 300 mg, taxoprexin (OD=120mg/kg/day x 5 days) or paclitaxel (OD=20mg/kg/day x 5 days) were injected as a bolus through the tail vein  
10 on each of five successive days. Both drugs were dissolved in 10% cremophor EL/10% ethanol/80% saline. Tumor volume was estimated from tumor width and length. As in the previous experiment, paclitaxel retarded tumor growth for about four days (LCK=1.0). In contrast, taxoprexin completely eliminated all measurable tumors in seven out of eight mice (C/T=7/8) at 120 mg/kg/day x 5 days, and in four out of seven mice at 80 mg/kg/day x 5 days. Histological  
15 examination of the tissue where the tumors had showed no tumor cells, only scar tissue. These data show that taxoprexin is curative in this model.

Example 3: response of human NCI-H522 lung tumor to treatment with taxoprexin and paclitaxel in mice.

The Southern Research Institute studied the anti-tumor activity of taxoprexin against  
20 human NCI-H522 lung tumor growing in nude mice. The tumors were implanted sub-cutaneously. Tumor mass was determined by calculation from tumor length and width. The drugs were dissolved in 12.5% cremophor EL/12.5% ethanol/75% saline and delivered i.v. into the tail vein, once a day for 5 days, from day 15 to 19 after tumor implantation. The results show that taxoprexin at 50 mg/kg/day x 5 days and paclitaxel at 20 mg/kg/day x 5 days eliminated all  
25 measurable tumors in 10/10 mice.

Example 4: the pharmacokinetic parameters of taxoprexin and paclitaxel in rats.

Rats were dosed for three minutes with 6.8mg/kg of taxoprexin through the tail vein. The drug was dissolved in 10% cremaphor EL/10% ethanol/80% saline. The serum concentrations of both taxoprexin and paclitaxel were measured in a reverse phase HPLC assay. Pharmacokinetic  
30 parameters were calculated from these data. Taxoprexin has ~ 100 fold lower clearance rate and volume of distribution (see Table 1).

Table 1.

<i>Taxoprexin</i> <sup>®</sup> Pharmacokinetic Parameters in Rats			
Drug	Clearance	Plasma $t_{1/2}$ (hr) (n=3)	Volume of Distribution
Paclitaxel	28.2 ml/min/kg	4.8±2.6	4.3 L/kg
<i>Taxoprexin</i> <sup>®</sup>	0.3 ml/min/kg	4.8±0.1	0.058 L/kg

Example 5: plasma concentration of taxoprexin and paclitaxel in rats following I.V. administrations of taxoprexin.

Rats were given a 3 minute intravenous infusion of taxoprexin through the tail vein at 0 time. The drug was dissolved in 10% cremophor EL/10% ethanol/80% saline. The dose was 6.8 mg/kg. The concentrations in serum of both paclitaxel and taxoprexin as a function of time were measured in a reverse phase HPLC assay (see Table 2).

Table 2.

Paclitaxel and <i>Taxoprexin</i> <sup>®</sup> plasma concentration (ng/ml) following administration of <i>Taxoprexin</i> <sup>®</sup> in Rats		
Time (hr)	Paclitaxel	<i>Taxoprexin</i> <sup>®</sup>
0	200	100,000
1	100	95,000
2	70	90,000
5	40	70,000
24	10	40,000

Example 6: plasma and tumor concentrations of paclitaxel derived from an I.V. dose of 50 mg/kg of taxoprexin to mice bearing M 109 or M 5076 tumors.

Mice with tumors derived from M109 or M5076 were given a bolus dose of taxoprexin through the tail vein at 0 time. The drug was dissolved in 10% cremophor EL/10% ethanol/80% saline. Mice were sacrificed and tumors immediately excised as a function of time after injecting the drug. Tumor tissue was homogenized and paclitaxel extracted. The concentration of paclitaxel was measured in a reverse phase HPLC assay. Blood was collected at the same time intervals and the amount of paclitaxel determined. The results show that after 24 hours the concentration of paclitaxel derived from taxoprexin is about 3  $\mu$ M, 40 times higher than the plasma concentration, 70 nM. Each data point is the mean of three measurements (n=3). NOTE: Paclitaxel has a  $t_{1/2}$  of <8 hours in the same tumor system.

Example 7: dose comparisons (MTD and Est LD<sub>40</sub>) of taxoprexin and paclitaxel in various animal species except humans.



Dose comparisons for paclitaxel and taxoprexin were made in mice, rats and dogs. The maximum tolerated dose (MTD) for mice, rats and dogs were about 4-5 times higher for taxoprexin than for paclitaxel on a mg/kg basis, or 3-3.5 times higher on a molar paclitaxel equivalent basis. Dose limiting toxicity for rats and dogs is due to decreases in platelets, neutrophils and lymphocytes. Taxoprexin is less toxic to mice, rats and dogs than is paclitaxel (see Table 3).

**Table 3.**

Dose Comparisons: Paclitaxel vs. <i>Taxoprexin</i> <sup>®</sup> in various species				
Species	Dose (mg/kg)*		Dose ratio: <i>Taxoprexin</i> <sup>®</sup> /Paclitaxel	
	<i>Taxoprexin</i> <sup>®</sup>	Paclitaxel	Based on Weight	Based on Taxane Molarity**
Mouse	MTD = 100 x 5 = 500	MTD = 20 x 5 = 100	5	3.6
Rat	Est LD <sub>40</sub> = 420	LD <sub>40</sub> = 85	5	3.6
Dog	MTD = 80	Est MTD = 20	4	2.9
<i>Average</i>			<i>4.7</i>	<i>3.4</i>

\* MTD is Maximum Tolerated Dose

\*\*MW of *Taxoprexin*<sup>®</sup> = 1164; MW of Paclitaxel = 854; MW ratio = 0.73

The foregoing data establish, surprisingly, safety implications of dose and pharmacokinetic advantages of taxoprexin. The higher MTD of taxoprexin compared to paclitaxel is believed to lead to greater safety of taxoprexin with much greater efficacy. The smaller volume of distribution for taxoprexin is believed to lead to less damage by taxoprexin in peripheral tissues including, but not limited to, nerves, hair follicles, GI cells, etc. The longer residence time of taxoprexin in tumors is believed to lead to fewer required dosing cycles for optimum therapeutic efficacy, which is believed to lead to decreased systemic toxicity. Taxoprexin thus appears to have a 100 fold lower clearance rate and volume of distribution than paclitaxel. In addition, levels of paclitaxel in tumors treated with taxoprexin remain stable for 24 hours, whereas such levels in tumors treated with paclitaxel have stable levels for less than 8 hours. Finally, taxoprexin was shown to cure 3/8 mice of the human HCT colon tumor, while paclitaxel cured 0/8. HCT is a paclitaxel resistant tumor.

#### Human Subject Experiments: Examples 8-9

#### Materials and methods:

##### *Administration before TAXOPREXIN<sup>®</sup> infusion (courses 1 and 2)*

Prior to receiving courses 1 and 2, patients received the following premedications in order to

-40-

minimize allergic reaction to the cremophor constituent of the *Taxoprexin*<sup>®</sup> infusion. Such pre-administration protocols associated with cremophor-containing medications are well known in the art. An example is as follows:

- |                        |                                                          |
|------------------------|----------------------------------------------------------|
| Dexamethasone          | 20 mg PO at 12 hours prior and 20 mg PO at 6 hours prior |
| 5 Diphenhydramine      | 50 mg IV push 30-60 minutes prior                        |
| H <sub>2</sub> blocker | IV 30-60 minutes prior                                   |
|                        | (e.g., Cimetidine 300 mg)                                |

*Alternative premedications (courses 3 and beyond)*

- If there are no allergic reactions in courses 1 and 2, subsequent courses may use the following alternative premedications, at the discretion of the Investigator:

- |                        |                                                                    |
|------------------------|--------------------------------------------------------------------|
| Dexamethasone          | EITHER: 1) 8 mg PO at 12 hours prior and 8 mg PO at 6 hours prior, |
|                        | OR                                                                 |
|                        | 2) 10 mg IV 30-60 minutes prior                                    |
| 15 Diphenhydramine     | 25 mg IV push 30-60 minutes prior                                  |
| H <sub>2</sub> blocker | IV 30-60 minutes prior                                             |
|                        | (e.g., Cimetidine 300 mg)                                          |

*Dilution of TAXOPREXIN<sup>®</sup> for IV Administration in Humans:*

- Two different vials are provided. The first vial, *TAXOPREXIN<sup>®</sup> CONCENTRATE* ("Concentrate"), contains 200 mg of DHA-paclitaxel in ethanol at a concentration of 100 mg/mL (2.0 mL total volume). The second vial, *DILUENT FOR Taxoprexin<sup>®</sup> Concentrate* ("Diluent"), contains 30 mL of a 4 to 1 (volume to volume) mixture of *Cremophor<sup>®</sup> EL-P* with ethanol. Prior to use, two (2) parts by volume of *Concentrate* are mixed with three (3) parts by volume of the *Diluent* in a sterile, dry, glass mixing bottle. The resulting "Preparation" of DHA-paclitaxel is then diluted into a standard IV infusion solution of 5% dextrose in water (D5W) or normal sterile saline (NS). The final concentration of DHA-paclitaxel in D5W or NS must be adjusted to be in the range of 0.8 to 8.0 mg/mL. *TAXOPREXIN<sup>®</sup>* is dosed on a body surface area basis. It is important to determine the proper body surface area (BSA) for the patient's height and weight (prior to each cycle of administration).

30 First Dilution: Premix Preparation

1. The appropriate number of vials of *Concentrate* are removed from the refrigerator. The vials are allowed to stand at room temperature for one (1) hour. Each vial is inspected to ensure that

-41-

the solution is clear and free of crystals or particulates. If particulates are present, the vials are sonicated at room temperature for thirty (30) seconds and reinspected. If crystals are present or if particulates remain following sonication, the vials are discarded.

2. Using a 21 gauge needle and a latex-free graduated syringe, sufficient in size to contain the required volume of *Concentrate*, the required dose of *Concentrate* is aseptically withdrawn sequentially from the *Concentrate* vials until the total volume is in the syringe.
3. The contents of the syringe are carefully dispersed into a sterile empty glass mixing bottle of sufficient size so that it can accommodate the total volume of *Concentrate* and *Diluent*, by slowly dripping the contents down the inside wall of the bottle to minimize foaming.
4. Using another 21 gauge needle and a latex-free graduated syringe of sufficient size so that it can accommodate the required volume of *Diluent*, a volume of *Diluent* equal to 1.5 times the volume of *Concentrate* is withdrawn.
5. The contents of the syringe containing the *Diluent* are carefully dispersed into the mixing bottle, by slowly dripping the contents down the inside wall of the bottle to minimize foaming.
6. The combined contents of the mixing bottle are gently rotated to assure complete mixing of the *Concentrate* and *Diluent*. This yields a premix *Preparation* concentration of 40 mg DHA-paclitaxel/mL.
7. The *TAXOPREXIN*<sup>®</sup> premix *Preparation* (40 mg DHA-paclitaxel/mL) should be clear; however, there may be some foam on top of the solution due to the *Cremophor*<sup>®</sup> EL-P. The premix *Preparation* is allowed to stand for five (5) minutes until most of the foam dissipates prior to continuing the dilution process.

Final Dilution: Infusion Solution

1. The entire contents of the *TAXOPREXIN*<sup>®</sup> premix *Preparation* (40 mg DHA-paclitaxel/mL) are aseptically transferred using a new 21 gauge needle and a latex-free syringe into a glass infusion bottle of either D5W or NS, of sufficient volume to produce a final infusion solution concentration between 0.8 and 8.0 mg DHA-paclitaxel/mL.
2. The infusion solution is thoroughly mixed by manual rotation.
3. As with all parenteral products, *TAXOPREXIN*<sup>®</sup> is inspected visually for particulate matter or discoloration prior to administration. If the *TAXOPREXIN*<sup>®</sup> premix *Preparation* or infusion solution is not clear or appears to be precipitation, the solution should not be used.

The *TAXOPREXIN*<sup>®</sup> infusion solution is administered intravenously over a period of two (2) hours under ambient room temperature and lighting conditions. The rate of administration

depends on the final volume of the final infusion solution, and a person of ordinary skill can easily determine such rate.

Storage and Stability:

Unopened vials of *Taxoprexin*<sup>®</sup> CONCENTRATE are stored in a refrigerator at 2-8°C (36-46°F), in their original package, to protect from light. Unopened vials of DILUENT for *Taxoprexin*<sup>®</sup> Concentrate are stored in their original package at controlled room temperature (15-30°C). *TAXOPREXIN*<sup>®</sup> premix Preparation (40 mg DHA-paclitaxel/mL) and fully prepared *TAXOPREXIN*<sup>®</sup> infusion solution, in either D5W or NS, are (and must be) used within 24 hours following removal of the *Taxoprexin*<sup>®</sup> CONCENTRATE vials from the refrigerator. Opened or premixed vials of *TAXOPREXIN*<sup>®</sup> or *TAXOPREXIN*<sup>®</sup> infusion solution must not be frozen or returned to a refrigerator.

How Supplied:

*Taxoprexin*<sup>®</sup> CONCENTRATE is supplied as 2.0 mL of a non-aqueous solution in a sterile, pyrogen-free, single-dose vial. DILUENT for *Taxoprexin*<sup>®</sup> CONCENTRATE (4:1 v/v mixture of *Cremophor*<sup>®</sup> EL-P and ethanol) is supplied as 30 mL of a sterile, pyrogen-free, single-dose vial.

In summary:

	Vial A: <i>Taxoprexin</i> <sup>®</sup> CONCENTRATE (DHA-paclitaxel in ethanol)	Vial B: DILUENT for <i>Taxoprexin</i> <sup>®</sup> (1:4, Ethanol: <i>Cremophor</i> <sup>®</sup> )
	200 mg/2 mL vial	3 mL in a 10 mL vial
	1,000 mg/10mL vial	15 mL in a 50 mL vial

Preparation and Administration Precautions:

Contact of the undiluted *Concentrate* with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may leach from PVC infusion bags or sets, diluted *TAXOPREXIN*<sup>®</sup> infusion solution is stored in glass bottles and administered through a polyethylene-lined Omni-Flow nitroglycerine administration set using an Abbott No. 4524 in-line latex-free high-pressure filter with a 0.22 micron microporous membrane.

*TAXOPREXIN*<sup>®</sup> is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing *TAXOPREXIN*<sup>®</sup> solutions. Procedures for the proper handling and disposal of anticancer drugs should be used. The use of gloves is recommended. If *Taxoprexin*<sup>®</sup> CONCENTRATE, premix Preparation, or infusion solution should come into contact with the skin or mucosa, immediately and thoroughly wash the

-43-

affected area with soap and water. Several guidelines on this subject have been published (*Am. J. Hosp. Pharm* 1986;43(5):1193-1204; *Am J. Hosp. Pharm.*, 1990;47(5):1033-1049; *JAMA* 1985;253(11):1590-1592; *ONS* 1988;2-14; *NIH Publication No. 83-2621*; National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents.

- 5 Available from Louis P. Jeffry, ScD, Chairman, National Study Commission and Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115; *Med. J. Austr.* 1983;1:426-428; *CA - A Cancer Journal for Clinicians* 1983;33(5):258-263).

Example 8: the pharmacokinetic parameters of Taxoprexin® in human subjects.

- 10 All statistical analysis was performed using WinNonlin v.2.0 software (Pharsight, Inc., Mountain View, CA, USA).

**Table 4.**

<i>Taxoprexin</i> ® Pharmacokinetic Parameters				
Patient ID	Dose (mg/m <sup>2</sup> )	C <sub>max</sub> (µg/mL)	AUC (µg x hr/mL)	% AUC Extrapolated
1	200	110	1433	12
2	400	115	1845	23
3	400	150	3710	59
4	660	138	8527	71
5	660	183	5563	43
6	660	279	8825	56
8	660	179	5117	48
9	660	211	5811	46
7	880	326	9091	46

Abbreviations: maximum plasma concentration (C<sub>max</sub>), area under the concentration-time curve (AUC).

15

**Table 5.**

<i>Taxoprexin</i> ® Pharmacokinetic Parameters				
Patient ID	Dose (mg/m <sup>2</sup> )	t <sub>1/2</sub> (hr)	V <sub>ss</sub> (L)	Cl (mL/min)
1	200	7.8	2.7	4.2
2	400	10	5.1	6.0
3	400	31	8.3	3.2
4	660	52	9.5	2.1
5	660	21	6.9	3.6
6	660	26	5.2	2.2
8	660	24	7.8	4.1
9	660	24	8.3	4.1
7	880	23	6.6	3.5

-44-

All Dose Levels                      24 (13)                      6.7 (2.1)                      3.7 (1.2)

Values are mean (SD). Abbreviations: terminal half-life ( $t_{1/2}$ ) volume of distribution at steady state ( $V_{ss}$ ); systemic clearance (Cl).

### Taxoprexin® Pharmacokinetic Conclusions

DHA-paclitaxel has a small volume of distribution (~7 L), low clearance (~4 mL/min) and a long terminal half-life (~24 hours, ~30% longer terminal  $t_{1/2}$  than paclitaxel alone).

5 DHA-paclitaxel exposure increased with increasing doses of *Taxoprexin®* DHA-paclitaxel

Example 9: the pharmacokinetic parameters of paclitaxel following administration of *Taxoprexin®* in human subjects.

10 **Table 6.**

Paclitaxel Pharmacokinetic Parameters Following Administration of <i>Taxoprexin®</i>						
Patient ID	Dose (mg/m <sup>2</sup> )	C <sub>max</sub> (ng/mL)	AUC (ng*hr/mL)	t <sub>1/2</sub> (hours)	Time > 0.05µM (hours)†	Paclitaxel: Taxoprexin AUC Ratio (%)
1	200	40	---	---	2	---
2	400	21	---	---	0	---
3	400	74	---	---	3	---
4	660	68	1596	32	3	0.019
5	660	61	1576	35	3	0.028
6	660	251	2209	20	16	0.025
8	660	73	4479	81	5	0.088
9	660	192	2592	46	4	0.045
7	880	134	2433	27	8	0.027

Abbreviation: maximum plasma concentration (C<sub>max</sub>), area under the concentration-time curve (AUC).

† Value from visual inspection of the plasma concentration-time curve.

**Table 7.**

Paclitaxel Pharmacokinetic Parameters Following Administration of <i>Taxoprexin®</i> and Paclitaxel*: A Comparison			
Schedule	C <sub>max</sub> (µM)	AUC (µM-h)	t > 0.05µM (hours)
IV TAXOPREXIN			
200 mg/m <sup>2</sup> (n = 1)	0.047	----	2.0†
400 mg/m <sup>2</sup> (n = 2)	0.056 ± 0.045	----	2.5†
660 mg/m <sup>2</sup> (n = 5)	0.15 ± 0.10	2.9 ± 1.4	6.1 ± 5.6†
880 mg/m <sup>2</sup> (n = 1)	0.16	2.9	> 8.0†

IV PACLITAXEL

-45-

1 hour (80-108 mg/m <sup>2</sup> ) <sup>1</sup>	4.5 ± 1.7	----	> 6.0
3 hours (175 mg/m <sup>2</sup> ) <sup>2</sup>	5.9 ± 0.9	19 ± 3.0	24 ± 3.5
24 hours (175 mg/m <sup>2</sup> ) <sup>2</sup>	0.5 ± 0.1	16 ± 4.4	34 ± 5.8
96 hours (140 mg/m <sup>2</sup> ) <sup>3</sup>	0.060 ± 0.003**	----	----

\* values represent mean ± SD

\*\* C<sub>ss</sub>

† Values obtained from inspection of the plasma concentration-time curve

1. Seidman, et al., *J. Clin. Oncol.*, 19982. Gianni, et al., *J. Clin. Oncol.*, 19953. Wilson, et al., *J. Clin. Oncol.*, 1994Paclitaxel Pharmacokinetics Conclusions

Paclitaxel exposure represented < 1% of taxoprexin.

Pharmacologically-relevant paclitaxel plasma concentrations (> 0.05 µM) were approached following treatment with taxoprexin at 660 & 880 mg/m<sup>2</sup>.

5 At the 660 mg/m<sup>2</sup> dose level interpatient variability in paclitaxel exposure was ~3 to 4-fold.

Paclitaxel t<sub>1/2</sub> appeared to be prolonged (mean ± SD, 40 ± 22 hrs) following treatment with taxoprexin.

The time plasma concentrations remain above a threshold concentration (e.g., 0.01 µM) may be related to neutropenia.

10 All references disclosed herein are incorporated by reference.

We claim as follows:

Claims

1. A fatty acid-anticancer compound conjugate composition for administration to a subject, comprising at least one fatty acid-anticancer compound conjugate in a container for administration to a subject, wherein the amount of the fatty acid-anticancer compound in the container is at least  
5 about 10% greater than the maximum tolerated dose (MTD) for the unconjugated at least one anticancer compound.
2. The fatty acid-anticancer compound conjugate composition of claim 1, wherein the amount in the container is at least about 20% greater than the MTD for the unconjugated at least one anticancer compound.
- 10 3. The fatty acid-anticancer compound conjugate composition of claim 1, wherein the amount in the container is at least about 30% greater than the MTD for the unconjugated at least one anticancer compound.
4. The fatty acid-anticancer compound conjugate composition of claim 1, wherein the amount in the container is at least about 40% greater than the MTD for the unconjugated at least one  
15 anticancer compound.
5. The fatty acid-anticancer compound conjugate composition of claim 1, wherein the amount in the container is at least about 50% greater than the MTD for the unconjugated at least one anticancer compound.
6. The fatty acid-anticancer compound conjugate composition of claim 1, wherein the amount  
20 in the container is at least about 75% greater than the MTD for the unconjugated at least one anticancer compound.
7. The fatty acid-anticancer compound conjugate composition of claim 1, wherein the amount in the container is at least about 100% greater than the MTD for the unconjugated at least one anticancer compound.
- 25 8. The fatty acid-anticancer compound conjugate composition of claim 1, wherein the amount in the container is at least about 200% greater than the MTD for the unconjugated at least one anticancer compound.



-47-

9. The fatty acid-anticancer compound conjugate composition of claim 1, wherein the amount in the container is at least about 300% greater than the MTD for the unconjugated at least one anticancer compound.
10. The fatty acid-anticancer compound conjugate composition of claim 1, wherein the amount in the container is at least about 400% greater than the MTD for the unconjugated at least one anticancer compound.
11. The fatty acid-anticancer compound conjugate composition of claim 1, wherein the container is a container for intravenous administration.
12. The fatty acid-anticancer compound conjugate composition of claim 1, wherein the anticancer compound is a taxane. .
13. The fatty acid-anticancer compound conjugate composition of claim 12, wherein the taxane is paclitaxel or docetaxel.
14. The fatty acid-anticancer compound conjugate composition of claim 1, wherein the conjugate is not encapsulated in a liposome.
15. The fatty acid-anticancer compound conjugate composition of claim 1, wherein the fatty acid is a C8-C26 unbranched, naturally occurring fatty acid.
16. The fatty acid-anticancer compound conjugate composition of claim 1, wherein the fatty acid is docosahexaenoic acid
17. A method for treating a subject having an abnormal mammalian cell proliferative disorder, comprising administering to the subject a fatty acid-anticancer compound conjugate composition in an amount which is at least about 10% greater than the maximum tolerated dose (MTD) for the unconjugated at least one anticancer compound.
18. The method of claim 17, wherein the amount of the fatty acid-anticancer compound conjugate composition administered is at least about 20% greater than the MTD for the unconjugated at least one anticancer compound.

19. The method of claim 17, wherein the amount of the fatty acid-anticancer compound conjugate composition administered is at least about 30% greater than the MTD for the unconjugated at least one anticancer compound.
20. The method of claim 17, wherein the amount of the fatty acid-anticancer compound conjugate composition administered is at least about 40% greater than the MTD for the unconjugated at least one anticancer compound.
21. The method of claim 17, wherein the amount of the fatty acid-anticancer compound conjugate composition administered is at least about 50% greater than the MTD for the unconjugated at least one anticancer compound.
22. The method of claim 17, wherein the amount of the fatty acid-anticancer compound conjugate composition administered is at least about 75% greater than the MTD for the unconjugated at least one anticancer compound.
23. The method of claim 17, wherein the amount of the fatty acid-anticancer compound conjugate composition administered is at least about 100% greater than the MTD for the unconjugated at least one anticancer compound.
24. The method of claim 17, wherein the amount of the fatty acid-anticancer compound conjugate composition administered is at least about 200% greater than the MTD for the unconjugated at least one anticancer compound.
25. The method of claim 17, wherein the amount of the fatty acid-anticancer compound conjugate composition administered is at least about 300% greater than the MTD for the unconjugated at least one anticancer compound.
26. The method of claim 17, wherein the amount of the fatty acid-anticancer compound conjugate composition administered is at least about 400% greater than the MTD for the unconjugated at least one anticancer compound.
28. The method of claim 17, wherein the anticancer compound is a taxane.
29. The method of claim 28, wherein the taxane is paclitaxel or docetaxel.
30. The method of claim 17, wherein the conjugate is not encapsulated in a liposome.

-49-

31. The method of claim 17, wherein the fatty acid is a C8-C26 unbranched, naturally occurring fatty acid.

32. The method of claim 17, wherein the fatty acid is docosahexaenoic acid.

33. A kit for administration of a fatty acid-anticancer compound conjugate composition to a  
5 subject, comprising

a container containing at least one fatty acid-anticancer compound conjugate, and  
instructions for administering the at least one fatty acid-anticancer compound conjugate  
to subject in need of such treatment in an amount which is at least about 10% greater than the  
maximum tolerated dose (MTD) for the unconjugated at least one anticancer compound.

10

34. The kit of claim 33, wherein the amount of the at least one fatty acid-anticancer compound  
conjugate is at least about 20% greater than the MTD for the unconjugated at least one anticancer  
compound.

35. The kit of claim 33, wherein the amount of the at least one fatty acid-anticancer compound  
15 conjugate is at least about 30% greater than the MTD for the unconjugated at least one anticancer  
compound.

36. The kit of claim 33, wherein the amount of the at least one fatty acid-anticancer compound  
conjugate is at least about 40% greater than the MTD for the unconjugated at least one anticancer  
compound.

20 37. The kit of claim 33, wherein the amount of the at least one fatty acid-anticancer compound  
conjugate is at least about 50% greater than the MTD for the unconjugated at least one anticancer  
compound.

38. The kit of claim 33, wherein the amount of the at least one fatty acid-anticancer compound  
conjugate is at least about 75% greater than the MTD for the unconjugated at least one anticancer  
25 compound.

39. The kit of claim 33, wherein the amount of the at least one fatty acid-anticancer compound  
conjugate is at least about 100% greater than the MTD for the unconjugated at least one anticancer  
compound.

-50-

40. The kit of claim 33, wherein the amount of the at least one fatty acid-anticancer compound conjugate is at least about 200% greater than the MTD for the unconjugated at least one anticancer compound.
41. The kit of claim 33, wherein the amount of the at least one fatty acid-anticancer compound conjugate is at least about 300% greater than the MTD for the unconjugated at least one anticancer compound.
42. The kit of claim 33, wherein the amount of the at least one fatty acid-anticancer compound conjugate is at least about 400% greater than the MTD for the unconjugated at least one anticancer compound.
43. The kit of claim 33, wherein the at least one fatty acid-anticancer compound conjugate is is a taxane. .
44. The kit of claim 43, wherein the taxane is paclitaxel or docetaxel.
45. The kit of claim 33, wherein the conjugate is not encapsulated in a liposome.
46. The kit of claim 33, wherein the fatty acid is a C8-C26 unbranched, naturally occurring fatty acid.
47. The kit of claim 33, wherein the fatty acid is docosohexaenoic acid.
48. A method for increasing the therapeutic index of anticancer compounds in a subject, comprising  
conjugating a fatty acid to an anticancer compound to form a fatty acid-anticancer compound conjugate; and  
administering the fatty acid-anticancer compound conjugate to the subject, whereby the therapeutic index of the anticancer compound is improved relative to non-conjugated formulations of the anticancer compound.
49. The method of claim 48, wherein the anticancer compound is a taxane. .
50. The method of claim 49, wherein the taxane is paclitaxel or docetaxel.
51. The method of claim 48, wherein the conjugate is not encapsulated in a liposome.

52. The method of claim 48, wherein the fatty acid is a C8-C26 unbranched, naturally occurring fatty acid.
53. The method of claim 52, wherein the fatty acid is docosohexaenoic acid.
54. The method of claim 48, wherein the subject is human.
- 5 55. A method for administering a fatty acid-taxane conjugate to a subject in need of such treatment, comprising infusing the conjugate in fewer than 3 hours.
56. The method of claim 55, wherein the conjugate is infused in 2 hours or less.
57. An injectable preparation of at least one fatty acid-taxane conjugate composition, comprising greater than about 6 mg/ml of the at least one fatty acid-taxane conjugate composition.
- 10 58. The injectable preparation of claim 57, wherein the preparation comprises greater than about 7 mg/ml of the at least one fatty acid-taxane conjugate composition..
59. The injectable preparation of claim 57, wherein the preparation comprises greater than about 8 mg/ml of the at least one fatty acid-taxane conjugate composition.
60. The injectable preparation of claim 57, wherein the preparation comprises greater than  
15 about 10 mg/ml of the at least one fatty acid-taxane conjugate composition.
61. The injectable preparation of claim 57, wherein the preparation comprises greater than about 15 mg/ml of the at least one fatty acid-taxane conjugate composition.
62. The injectable preparation of claim 57, wherein the preparation comprises greater than about 20 mg/ml of the at least one fatty acid-taxane conjugate composition.
- 20 63. The injectable preparation of claim 57, wherein the preparation comprises greater than about 40 mg/ml of the at least one fatty acid-taxane conjugate composition.
64. The injectable preparation of claim 57, wherein the preparation comprises greater than about 60 mg/ml of the at least one fatty acid-taxane conjugate composition.
- 25 65. The injectable preparation of claim 57, wherein the preparation comprises greater than about 80 mg/ml of the at least one fatty acid-taxane conjugate composition.

66. The injectable preparation of claim 57, wherein the preparation comprises greater than about 100 mg/ml of the at least one fatty acid-taxane conjugate composition.
67. The injectable preparation of claim 57, wherein the fatty acid is a C8-C26 unbranched, naturally occurring fatty acid.
- 5 68. The injectable preparation of claim 67, wherein the fatty acid is docosohexaenoic acid.
69. An injectable composition of at least one fatty acid-taxane conjugate, comprising less than about 0.3 mg/ml of the at least one fatty acid-taxane conjugate.
70. A fatty acid-taxane conjugate composition, comprising greater than about 6 mg/ml of at least one fatty acid-taxane conjugate, and a surfactant.
- 10 71. The fatty acid-taxane conjugate composition of claim 70, wherein the amount of the at least one fatty acid-taxane conjugate is greater than about 7 mg/ml.
72. The fatty acid-taxane conjugate composition of claim 70, wherein the amount of the at least one fatty acid-taxane conjugate is greater than about 8 mg/ml.
73. The fatty acid-taxane conjugate composition of claim 70, wherein the amount of the at least  
15 one fatty acid-taxane conjugate is greater than about 10 mg/ml.
74. The fatty acid-taxane conjugate composition of claim 70, wherein the amount of the at least one fatty acid-taxane conjugate is greater than about 15 mg/ml.
75. The fatty acid-taxane conjugate composition of claim 70, wherein the amount of the at least one fatty acid-taxane conjugate is greater than about 20 mg/ml.
- 20 76. The fatty acid-taxane conjugate composition of claim 70, wherein the amount of the at least one fatty acid-taxane conjugate is greater than about 40 mg/ml.
77. The fatty acid-taxane conjugate composition of claim 70, wherein the amount of the at least one fatty acid-taxane conjugate is greater than about 60 mg/ml.
- 25 78. The fatty acid-taxane conjugate composition of claim 70, wherein the amount of the at least one fatty acid-taxane conjugate is greater than about 80 mg/ml.

-53-

79. The fatty acid-taxane conjugate composition of claim 70, wherein the amount of the at least one fatty acid-taxane conjugate is greater than about 100 mg/ml.
80. The fatty acid-taxane conjugate composition of claim 70, wherein the fatty acid is a C8-C26 unbranched, naturally occurring fatty acid.
- 5 81. The fatty acid-taxane conjugate composition of claim 80, wherein the fatty acid is docosohexaenoic acid
82. The fatty acid-taxane conjugate composition of claim 70, wherein the surfactant is Cremophor EL or EL-P.
83. The fatty acid-taxane conjugate composition of claim 82, wherein the concentration of  
10 Cremophor is between about 9.6% and about 49.7% (vol/vol).
84. A fatty acid-taxane conjugate composition, comprising at least one fatty acid-taxane conjugate and a surfactant, wherein the ratio of the weight of the at least one fatty acid-taxane conjugate and volume of the surfactant is at least about 50 mg/ml.
85. The fatty acid-taxane conjugate composition of claim 84, wherein the ratio of the weight  
15 of the at least one fatty acid-taxane conjugate and volume of the surfactant is at least about 60 mg/ml.
86. The fatty acid-taxane conjugate composition of claim 84, wherein the ratio of the weight of the at least one fatty acid-taxane conjugate and volume of the surfactant is at least about 70 mg/ml.
- 20 87. The fatty acid-taxane conjugate composition of claim 84, wherein the ratio of the weight of the at least one fatty acid-taxane conjugate and volume of the surfactant is at least about 80 mg/ml.
88. The fatty acid-taxane conjugate composition of claim 84, wherein the ratio of the weight of the at least one fatty acid-taxane conjugate and volume of the surfactant is at least about 90  
25 mg/ml.

89. The fatty acid-taxane conjugate composition of claim 84, wherein the ratio of the weight of the at least one fatty acid-taxane conjugate and volume of the surfactant is at least about 100 mg/ml.
90. The fatty acid-taxane conjugate composition of claim 84, wherein the surfactant is  
5 Cremophor EL or EL-P.
91. The fatty acid-taxane conjugate composition of claim 84, wherein the fatty acid is a C8-C26 unbranched, naturally occurring fatty acid.
92. The fatty acid-taxane conjugate composition of claim 91, wherein the fatty acid is docosahexaenoic acid.
- 10 93. The fatty acid-taxane conjugate composition of claim 84, wherein the taxane is paclitaxel or docetaxel.
94. The fatty acid-taxane conjugate composition of claim 84, further comprising a solvent.
95. The fatty acid-taxane conjugate composition of claim 94, wherein the solvent is ethanol.
96. The fatty acid-taxane conjugate composition of claim 95, wherein the solvent and the  
15 surfactant are present in a ratio of about 1:1.
97. A fatty acid-taxane conjugate composition, comprising at least one fatty acid-taxane conjugate and a solvent, wherein the ratio of the weight of the at least one fatty acid-taxane conjugate and volume of the solvent is at least about 42 mg/ml.
98. The fatty acid-taxane conjugate composition of claim 97, wherein the ratio of the weight  
20 of the at least one fatty acid-taxane conjugate and volume of the solvent is at least about 50 mg/ml.
99. The fatty acid-taxane conjugate composition of claim 97, wherein the ratio of the weight of the at least one fatty acid-taxane conjugate and volume of the solvent is at least about 60 mg/ml.
100. The fatty acid-taxane conjugate composition of claim 97, wherein the ratio of the weight of the at least one fatty acid-taxane conjugate and volume of the solvent is at least about 70 mg/ml.



-55-

101. The fatty acid-taxane conjugate composition of claim 97, wherein the ratio of the weight of the at least one fatty acid-taxane conjugate and volume of the solvent is at least about 80 mg/ml.
102. The fatty acid-taxane conjugate composition of claim 97, wherein the ratio of the weight of the at least one fatty acid-taxane conjugate and volume of the solvent is at least about 100  
5 mg/ml.
103. The fatty acid-taxane conjugate composition of claim 97, wherein the solvent is Cremophor EL.
104. The fatty acid-taxane conjugate composition of claim 97, wherein the fatty acid is a C8-C26 unbranched, naturally occurring fatty acid.
105. The fatty acid-taxane conjugate composition of claim 104, wherein the fatty acid is  
10 docosahexaenoic acid.
106. The fatty acid-taxane conjugate composition of claim 97, wherein the taxane is paclitaxel or docetaxel.
107. The fatty acid-taxane conjugate composition of claim 97, further comprising a surfactant.
108. The fatty acid-taxane conjugate composition of claim 107, wherein the surfactant is  
15 Cremophor.
109. The fatty acid-taxane conjugate composition of claim 108, wherein the solvent and the surfactant are present in a ratio of about 1:1.
110. A fatty acid-taxane conjugate composition, comprising at least about 37 mg/ml of at least  
20 one fatty acid-taxane conjugate.
111. The fatty acid-taxane conjugate composition of claim 110, wherein the amount of the at least one fatty acid-taxane conjugate is least about 40 mg/ml.
112. The fatty acid-taxane conjugate composition of claim 110, wherein the amount of the at least one fatty acid-taxane conjugate is least about 50 mg/ml.

-56-

113. The fatty acid-taxane conjugate composition of claim 110, wherein the amount of the at least one fatty acid-taxane conjugate is least about 60 mg/ml.
114. The fatty acid-taxane conjugate composition of claim 110, wherein the amount of the at least one fatty acid-taxane conjugate is least about 80 mg/ml.
- 5 115. The fatty acid-taxane conjugate composition of claim 110, wherein the amount of the at least one fatty acid-taxane conjugate is least about 100 mg/ml.
116. The fatty acid-taxane conjugate composition of claim 110, wherein the fatty acid is a C8-C26 unbranched, naturally occurring fatty acid.
117. The fatty acid-taxane conjugate composition of claim 110, wherein the fatty acid is  
10 docosahexaenoic acid.
118. The fatty acid-taxane conjugate composition of claim 110, wherein the taxane is paclitaxel or docetaxel.
119. A method for treating a subject having an abnormal mammalian proliferative disorder, comprising:  
15 administering to the subject a fatty acid-taxane conjugate in an amount of the conjugate which is at least 250, 275, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1050, 1100, 1150, 1200, 1250, 1300, 1350 or 1400 mg/meter<sup>2</sup>.
120. The method of claim 119, wherein the amount is administered to the subject over a period  
20 of 24 hours or less, 6 hours or less, 3 hours or less, or 2 hours or less.
121. The method of claim 119, wherein the fatty acid is a C8-C26 fatty acid.
122. The method of claim 119, wherein the fatty acid is a C16-C22 unbranched, naturally  
25 occurring fatty acid.
123. The method of claim 119, wherein the fatty acid is linoleic acid, palmitic acid, arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid, 2-octanoate, 2-hexanoate, CH<sub>3</sub>-hexanoate, CH<sub>3</sub>-butanoate, or oleic acid.

124. The method of claim 123, wherein the fatty acid is linoleic acid, palmitic acid, arachidonic acid, eicosapentaenoic acid, or docosahexaenoic acid.

5 125. The method of any one of claims 119 - 124, wherein the taxane is paclitaxel.

126. The method of claim 125, wherein the fatty acid is conjugated at the 2' OH position of paclitaxel.

10 127. The method of claim 126, wherein the fatty acid is docosahexaenoic acid.

128. A composition of matter comprising:  
a substantially pure crystal of a conjugate of a C8-C26 fatty acid and an anti-cancer compound.

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129. The composition of matter of claim 128, wherein the fatty acid is a C16-C22 fatty acid.

130. The composition of matter of claim 129, wherein the fatty acid is a naturally-occurring, unbranched fatty acid.

20

131. The composition of matter of claim 129, wherein the fatty acid is linoleic acid, palmitic acid, arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid, 2-octanoate, 2-hexanoate, CH<sub>3</sub>-hexanoate, CH<sub>3</sub>-butanoate, or oleic acid.

25 132. The composition of matter of claim 129, wherein the fatty acid is is linoleic acid, palmitic acid, arachidonic acid, eicosapentaenoic acid, or docosahexaenoic acid.

133. The composition of matter of any one of claims 128 - 132, wherein the anti-cancer compound is a taxane.

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134. The composition of matter of claim 133, wherein the taxane is paclitaxel.

135. The composition of matter of claim 134, wherein the fatty acid is conjugated to paclitaxel at the 2' OH position.

136. The composition of matter of claim 135, wherein the fatty acid is docosahexaenoic acid.

137. A method for isolating a conjugate of a C8-C22 fatty acid and an anti-cancer compound comprising:

covalently conjugating the fatty acid and the anti-cancer compound to form the conjugate, forming a crystal of the conjugate, and

isolating the crystal.

138. The method of claim 137, wherein the fatty acid is an oil at room temperature.

139. The method of claim 137, wherein the fatty acid is a polyunsaturated fatty acid.

140. The method of claim 139, wherein the fatty acid is a C16-C22 fatty acid.

141. The method of claim 137, wherein the fatty acid is a C16-C22 unbranched, naturally-occurring fatty acid.

142. The method of claim 137, wherein the fatty acid is linoleic acid, palmitic acid, arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid, 2-octanoate, 2-hexanoate, CH<sub>3</sub>-hexanoate, CH<sub>3</sub>-butanoate, or oleic acid.

143. The method of claim 137, wherein the fatty acid is linoleic acid, palmitic acid, arachidonic acid, eicosapentaenoic acid, or docosahexaenoic acid.

144. The method of any one of claims 137 - 143, wherein the anti-cancer compound is a taxane.

145. The method of claim 144, wherein the taxane is paclitaxel.

146. The method of claim 145, wherein the fatty acid is conjugated to paclitaxel at the 2' OH

position of paclitaxel.

147. The method of claim 146, wherein the fatty acid is docosahexaenoic acid.

5 148. A kit comprising:  
a package containing  
a first container housing a solution of a conjugate of a fatty acid and a taxane dissolved in  
a first solvent,  
a second container causing a mixture of a second solvent and a surfactant, the second  
10 solvent miscible with the first solvent, and  
instructions for combining the solution and the mixture.

149. The kit of claim 148, wherein the first solvent is ethanol.

15 150. The kit of claim 148, wherein the surfactant is cremophor.

151. The kit of claim 148, wherein the second solvent is ethanol.

152. The kit of claim 151, wherein the cremophor is present in a ratio to the second solvent of  
20 at least 1:1, 2:1, 3:1, or 4:1.

153. The kit of any one of claims 148 - 152, wherein the fatty acid is a C8-C26 fatty acid, a  
C16-C22 fatty acid, or a naturally-occurring unbranched C16-C22 fatty acid.

25 154. The kit of any one of claims 148 - 152, wherein the fatty acid is linoleic acid, palmitic acid,  
arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid, 2-octanoate, 2-hexanoate, CH<sub>3</sub>-  
hexanoate, CH<sub>3</sub>-butanoate, or oleic acid.

155. The kit of any one of claims 148 - 152, wherein the fatty acid is linoleic acid, palmitic acid,  
30 arachidonic acid, eicosapentaenoic acid, or docosahexaenoic acid.

156. The kit of claim 153, wherein the taxane is paclitaxel.

157. The kit of claim 156, wherein the fatty acid is docosahexaenoic acid.
158. The kit of claim 152, wherein the concentration of the conjugate in the solvent is about 100  
5 mg/ml.
159. A pharmaceutical preparation comprising:  
an intravenous solution of a conjugate of a C8-C26 fatty acid and a taxane, wherein the  
solution is substantially free of liposomes.
- 10 160. The pharmaceutical preparation of claim 159, wherein the fatty acid is a C16-C22  
unbranched, naturally-occurring fatty acid.
161. The pharmaceutical preparation of claim 159, wherein the fatty acid is linoleic acid,  
15 palmitic acid, arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid, 2-octanoate, 2-  
hexanoate, CH<sub>3</sub>-hexanoate, CH<sub>3</sub>-butanoate, or oleic acid.
162. The pharmaceutical preparation of claim 159, wherein the fatty acid is linoleic acid,  
palmitic acid, arachidonic acid, eicosapentaenoic acid, or docosahexaenoic acid.
- 20 163. The pharmaceutical preparation of any one of claims 159 - 162, wherein the taxane is  
paclitaxel.
164. The pharmaceutical preparation of claim 163, wherein the fatty acid is conjugated to the  
25 paclitaxel at the 2' OH position of paclitaxel.
165. The pharmaceutical preparation of claim 164, wherein the fatty acid is docosahexaenoic  
acid.
- 30 166. A method for preparing an intravenous solution for administration to a subject having a  
mammalian cell proliferative disorder comprising:  
combining (a) a solution of a conjugate of a fatty acid and a taxane dissolved in a first

-61-

solvent, and (b) a mixture of a second solvent and a surfactant, the second solvent miscible with the first solvent, and said combining resulting in a pre-mix, and adding the pre-mix to an intravenous solution.

5 167. The method of claim 166, wherein the first solvent is ethanol.

168. The method of claim 166, wherein the surfactant is cremophor.

169. The method of claim 166, wherein the second solvent is ethanol.

10

170. The method of claim 168, wherein the cremophor is present in a ratio to the second solvent of at least 1:1, 2:1, 3:1 or 4:1.

15

171. The method of any one of claims 166 - 170, wherein the fatty acid is a C8-C26 fatty acid, a C16-C22 fatty acid or a naturally-occurring unbranched C16-C22 fatty acid.

172. The method of any one of claims 166 - 170, wherein the fatty acid is linoleic acid, palmitic acid, arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid, 2-octanoate, 2-hexanoate, CH<sub>3</sub>-hexanoate, CH<sub>3</sub>-butanoate, or oleic acid.

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173. The method of any one of claims 166 - 170, wherein the fatty acid is linoleic acid, palmitic acid, arachidonic acid, eicosapentaenoic acid, or docosahexaenoic acid.

174. The method of claim 171, wherein the taxane is paclitaxel.

25

175. The method of claim 174, wherein the fatty acid is docosahexaenoic acid and the fatty acid is conjugated to the 2' OH position of paclitaxel.

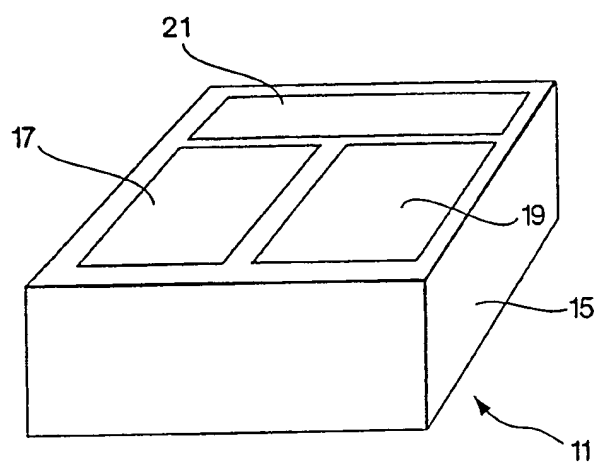


Fig. 1